THE TEDDY BEAR BOOK

Pediatric Injectable DRUGS

TENTH EDITION

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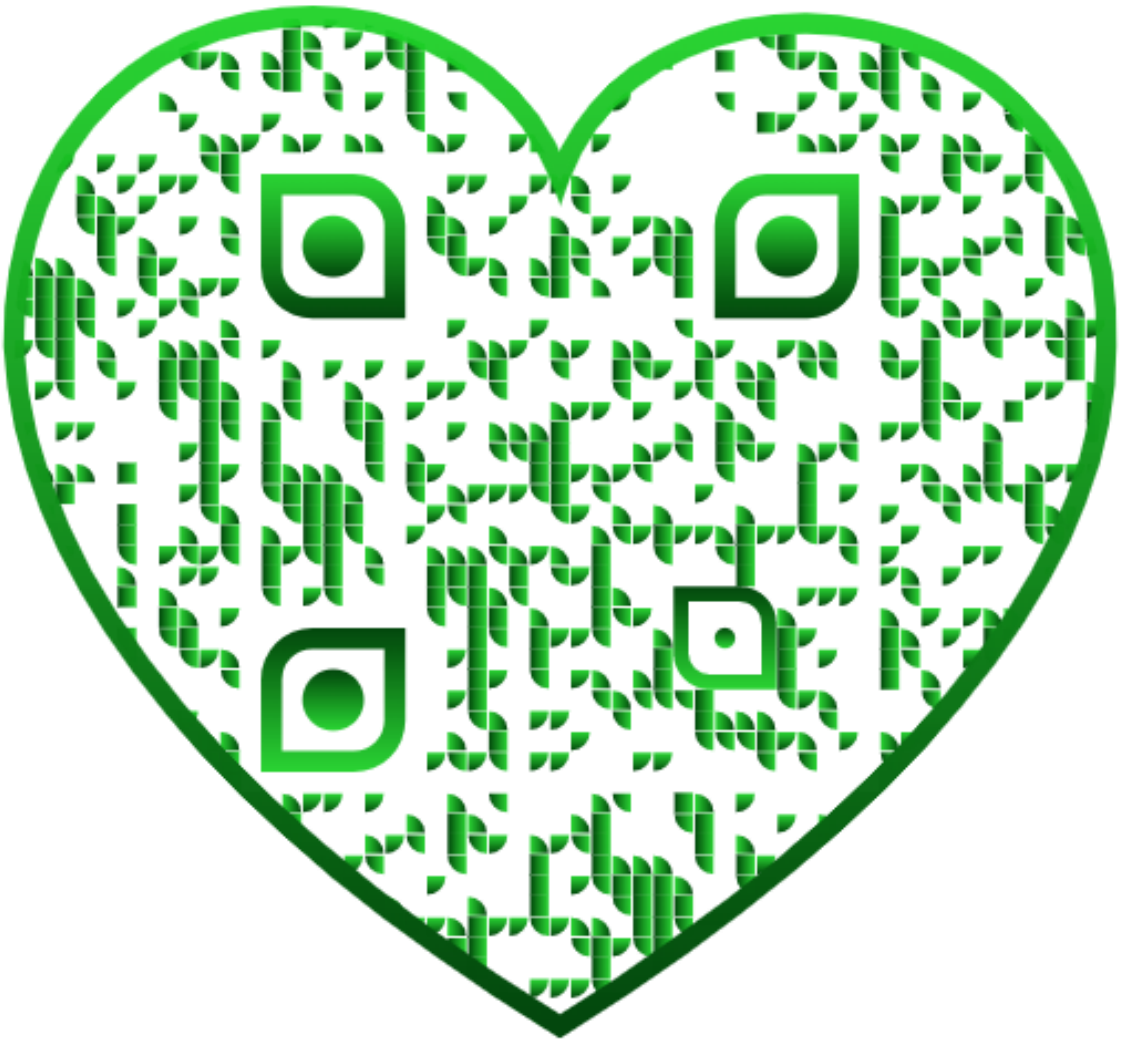

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Dedication

This edition is dedicated to our families who sacrificed a tremendous amount of "quality time" to make it possible for us to participate in this project. We are forever indebted to them, and to our friends and loved ones for their patience, encouragement, motivation, and endless support.

Publisher's Note

This QR code will enable you to check for any updates or corrections that have been issued on this edition as well as information about the forthcoming mobile app. You can also visit www.ashp.org/teddybear to access updates, corrections, and information about the forthcoming mobile app.

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Preface

In the late 1930s, elixir sulfanilamide was marketed for the treatment of streptococcal infections. The poor solubility of the antibiotic made it difficult to create a liquid formulation; hence, the medication was mixed with diethylene glycol. Although the company tested the raspberry-flavored product for palatability, it was not tested for safety before distribution. *Unfortunately*, more than 100 individuals, including many children, died following its ingestion. In 1949, intravenous chloramphenicol, a bacteriostatic antimicrobial, became an important agent in the treatment of a variety of pediatric infectious diseases. *Unfortunately*, the medication caused significant vomiting, ashen-gray color of the skin, limp body tone, distended abdomen, hypotension, and cardiovascular collapse. This phenomenon, termed *gray-baby syndrome*, resulted in the death of hundreds of newborns who lacked the hepatic enzymes (i.e., UDP-glucuronyl transferase) necessary to metabolize large doses of the medication and the required renal maturity to excrete the unconjugated drug. Thalidomide was introduced in the late 1950s as a sleeping pill but was quickly noted to prevent nausea and vomiting during early pregnancy. *Unfortunately*, it was subsequently found to cause significant birth defects and was removed from the market. In 1983, the intravenous vitamin E supplement, E-Ferol, was marketed. *Unfortunately*, within 3 months, its use was associated with ascites, liver and renal failure, thrombocytopenia, and death in low birth weight infants. This tragedy was ultimately attributed to the polysorbates added as emulsifiers; a new drug application had not been submitted to the Food and Drug Administration (FDA) prior to use. *Unfortunately*, there are other noteworthy therapeutic disasters including valproate hepatotoxicity in young children, aspirin and Reye syndrome, benzyl alcohol and fatal gasping syndrome, and the list goes on. The negative effects of these therapeutic disasters have led to more structured drug regulations and control over drug use and development including passage of the 1938 Federal Food, Drug, and Cosmetic Act.

Regardless of profession, those practicing in pediatrics understand that the vast majority of medications given are used off label. In fact, as much as 75% of all medications used in this population are not approved by the FDA for use in either the specific age group or disease for which it is administered. Despite the National Institutes of Health's creation of the Pediatric Pharmacology Research Units (PPRUs) and the FDA Modernization Act (FDAMA), much of the necessary research to validate safety and efficacy of medications has yet to be conducted in all pediatric populations. The impact of FDAMA has been important as more than 100 industry-sponsored studies have been conducted, but much of the effort has not included premature and full-term neonates and infants.

The reasons for lack of information and subsequent FDA approval is multifactorial and relates to priorities in pharmaceutical industry and federal funding, the belief that we need to protect our most vulnerable from medication-associated harm, and ethical considerations such as voluntary participation and informed consent/assent, which in many cases is not possible to obtain due to the patient's young age. All stakeholders must continue to proactively discuss the issues that surround drug research and prevention of therapeutic misadventures in the pediatric population.

The tenth edition of *Pediatric Injectable Drugs (The Teddy Bear Book)* has three new editors. Collectively, these editors bring 75 years of pediatric pharmacy practice experience to the book and represent the practice approaches and philosophies of three different institutions. Beyond general pediatric pharmacotherapy, the specific expertise of the editors includes critical care medicine, hematology and oncology, infectious diseases, and neurology.

This edition of *Pediatric Injectable Drugs (The Teddy Bear Book)* has been revised to include 238 parenteral medications. Twenty new monographs, some of which are newly marketed drugs, have been added. Previously published monographs have been extensively reviewed and updated to include the most recent literature available. Information included in this text was compiled in an evidence-based manner from, in most cases, the primary literature

including case reports, observational reports, and comparative trials. Limited information is available for some of the frequently used older drugs in which case recommendations may come from textbooks. Importantly, the references are provided in the back of the book according to generic drug names, thereby allowing readers to access the source of the information provided and make independent decisions related to their specific patients.

With this edition, *Pediatric Injectable Drugs (The Teddy Bear Book)* will also be available as both a mobile app and as an eBook. For information on the mobile app, go to www.ashp.org/teddybear. The eBook version of *Pediatric Injectable Drugs (The Teddy Bear Book)* can be purchased through ASHP eBooks (ebooks.ashp.org) or from Amazon Kindle, the Apple iBookstore, or Barnes & Noble Nook.

We hope that this text improves your ability to safely and effectively use medications in all members of the pediatric community and that ultimately the information contained in this reference will not only facilitate their recovery, enhance their quality of life, and prevent *unfortunate* therapeutic misadventures, but also enable you to sleep better at night.

Stephanie J. Phelps
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Kelley R. Lee
A. Jill Thompson
2013

Introduction

The following guidelines were developed to provide a single authoritative source of information on the parenteral administration of medications to pediatric patients. All recommendations should be individualized in accordance with the clinical situation.

This tenth edition of ASHP's *Pediatric Injectable Drugs* has been updated to improve existing sections and to make them more user-friendly through their placement in the monograph and with the addition of more specific subheadings. The tenth edition provides the following information for updates to 238 drugs and all references that support information contained in the text.

Brand names

Common brand names and, if applicable, other names (synonyms) are listed.

Medication error potential

If the drug was included in the ISMP's *List of High-Alert Medications*, ISMP's *List of Confused Drug Names*, or the USP's *Findings of Look-alike and/or Sound-alike Drug Errors* at the time the monograph was written, it will be noted in this section. Tall man letters, per FDA and ISMP recommendations, will be used in this section, as well as in the monograph title and in the title in the references, if applicable.

Contraindications and warnings

While it may be noted in the monographs, it is understood that a drug would be contraindicated in a patient who has experienced a prior anaphylaxis or type I hypersensitivity reaction. U.S. Boxed Warnings, Contraindications, and Other Warnings, if applicable, will be described under subheadings in this section. The Other Warnings subheading will describe warnings deemed noteworthy and may not be the complete list of warnings included in the manufacturer's labeling. It is recommended to review the labeling for the most complete list.

Infusion-related cautions

Warnings are provided where appropriate. If a drug requires premedication or if the administration of the drug necessitates the availability of another drug (i.e., to have on hand), information regarding premedication or the drug to have on hand will be provided in this section. If a drug should be given only via central access, this will be noted here. If a drug carries an increased risk of thrombophlebitis, infiltration, or extravasation, it will be noted in this section. Appendix E provides information regarding extravasation treatment for medications known to cause effects from infiltration or extravasation.

Dosage

Unless otherwise specified, dosages are for all age groups. These age groups are as follows: neonates (premature and term), up to 1 month; infants, 1–24 months; children, 2–12 years, and adolescents, 12–18 years. When applicable, *adult* dosing is also provided. While these age groups provide general guidelines for therapy in pediatric patients, it should be noted that changes in development, which affect drug pharmacokinetics and pharmacodynamics, and hence, dosing recommendations, are not confined to the limits of these defined age groups.

Dosage is often expressed as X mg/kg/day divided q Y–Z hours, where the total daily dose (X) is given in equally divided doses at evenly spaced intervals. Dosage may also be expressed as X mg/m^2/day divided q Y–Z hours, a calculation of body surface area (BSA) as determined from height and mass. See Appendix A for a BSA nomogram.

The presence of obesity may require the practitioner to estimate ideal body mass/weight and calculate an adjusted weight for the dosing of some medications. Appendix B provides a nomogram for estimating total body mass/weight.

Dosage adjustment in organ dysfunction

Drugs requiring dosage adjustment in patients with renal or hepatic dysfunction and serum drug concentration monitoring are indicated. The manufacturer's labeling and specialized references are provided when available. Information, if known, will also be included about dosage adjustment or therapeutic drug monitoring with dialysis, continuous renal replacement therapy, and with extracorporeal membrane oxygenation.

Maximum dosage

Maximum dosages are referenced to primary literature where available. However, maximum dosages for pediatric patients are often extrapolated from *adult* data because of a lack of documented experience with pediatric patients. Many manufacturers caution against exceeding the maximum recommended *adult* dosage (usually expressed as X g/day) in pediatric patients. In this reference, when the maximum dosage is expressed as "mg/kg/day, not to exceed X g/day," "X g/day" is typically the manufacturer's maximum recommended *adult* dosage and should be used only as an upper limit for pediatric dosing. It should not be inferred that use of these maximum dosages in pediatric patients is recommended and is without risk of toxicity. Readers should consult the references indicated for information on the use of these maximum dosages in the pediatric population.

Additives

Pertinent additives, including sodium and those with a potential for toxicity or adverse effects, are listed. Please see Appendix C for specific information on common additives with a potential for toxicity or adverse effects.

Suitable diluents

If a drug can be mixed or diluted with a fluid, the appropriate fluids will be listed here. Compatible drugs will NOT be listed.

Drug stability in some of the IV solutions listed is limited. The manufacturer's labeling and specialized references (e.g., Trissel LA. *Handbook on Injectable Drugs*. 17th ed. Bethesda, MD: American Society of Health-System Pharmacists; 2013) should be consulted for detailed stability information.

Maximum concentration

Generally, any concentration up to the maximum may be administered, taking into consideration the patient's fluid status (and potential for loss of vascular access), administration method (IV push vs. intermittent infusion), drug administration rate (and drug administration device flow rate range, if applicable), dose (and degree of accuracy required in dose measurement), and drug stability. However, some drugs, as indicated in these guidelines, should not be diluted.

For drugs available as solutions that may be administered undiluted, the maximum concentration is the commercially available concentration. For drugs that must be reconstituted prior to administration, the maximum concentration should serve as a guide for the minimum dilution required.

Concentrations listed are referenced to literature on drug use in pediatric patients to the extent possible. However, concentrations administered to *adults* are cited where documentation on use in pediatric patients is insufficient. The references should be consulted. The IV Push, Intermittent Infusion, Continuous Infusion, and Other Routes of Administration sections all begin with information concerning the concentration or concentration range usual for that method or route of administration.

Preparation and delivery

When pertinent, issues related to preparation and delivery are included in this section and, if applicable, will be described under the following subheadings: Preparation, Delivery, Stability, Compatibility, and Photosensitivity. If a drug has information regarding compatibility with parenteral nutrition solutions, a statement will be included. Appendix D provides information regarding compatibility of medications with parenteral nutrition solutions.

IV push

This rate is generally expressed as a period of time over which the dose should be administered (seconds or minutes) or as a quantity of drug per unit of time. In the latter case, the size of the dose determines the administration time. For the purpose of this text, IV push is defined as <5 minutes. Drugs for which IV push administration is contraindicated are noted.

Intermittent infusion

The recommended infusion rate is expressed as a period of time over which the dose should be administered (minutes to hours) or as a quantity of drug per unit of time (size of dose determines administration time).

Continuous infusion

The recommended infusion rate is usually expressed as a quantity of drug per unit of time; infusion is continued for 24 hours unless otherwise specified (e.g., until the desired therapeutic endpoint is achieved).

Other routes of administration

This section contains information on the appropriateness of other routes of administration, including IM, SC, ET, IT, and IO administration and the best site for administration. The terms *contraindicated* and *not recommended* will be used. *Contraindicated* implies that you do not administer the drug in that manner. *Not recommended* implies that it may have been administered in that manner, but it is not recommended to administer it in that manner. Drugs for which other routes of administration are contraindicated are noted.

Comments

Miscellaneous information is included when pertinent. Information pertaining to *adults* is sometimes included because, in the absence of reports on pediatric use, *adult* data may be relevant and may be cautiously extrapolated to the pediatric population.

When applicable, the following subheadings may be included in the comments section: Significant Adverse Effects, Rare Adverse Effects, Monitoring, Drug Interactions, Pharmacokinetic Considerations, Pharmacodynamic Considerations, Laboratory Interference, Osmolality, and Other.

Abbreviations

Solutions:

ABS	acrylonitrile, butadiene, and styrene
BW	bacteriostatic water for injection
D-LR	dextrose—Ringer's injection, lactated, combinations
D-R	dextrose—Ringer's injection combinations
D-S	dextrose—saline combinations
D10NS	dextrose 10% in sodium chloride 0.9%
D10W	dextrose 10% in water
D15W	dextrose 15% in water
D20W	dextrose 20% in water
D2.5W	dextrose 2.5% in water
D2.5½NS	dextrose 2.5% in sodium chloride 0.45%
D5LR	dextrose 5% in Ringer's injection, lactated
D5NS	dextrose 5% in sodium chloride 0.9%
D5¼NS	dextrose 5% in sodium chloride 0.225%
D5⅓NS	dextrose 5% in sodium chloride 0.3%
D5½NS	dextrose 5% in sodium chloride 0.45%
D5R	dextrose 5% in Ringer's injection
D5S	dextrose 5% in sodium chloride 0.9%, 0.45%, 0.3%, or 0.225%
D5W	dextrose 5% in water
LR	Ringer's injection, lactated
NS	sodium chloride 0.9% (normal saline)
¼NS	sodium chloride 0.225% (¼ normal saline)
⅓NS	sodium chloride 0.3% (⅓ normal saline)
½NS	sodium chloride 0.45% (½ normal saline)
R	Ringer's injection
SW	sterile water for injection

Terms:

AAP	American Academy of Pediatrics
ABCD	amphotericin B colloidal dispersion
ABS	acrylonitrile, butadiene, and styrene
ABW	actual body weight
ACCP	American College of Chest Physicians
ACLS	advanced cardiovascular life support
ACT	activated clotting time
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
AED	antiepileptic drug
AHA	American Heart Association
AHF	antihemophilic factor
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphocytic leukemia

ALT	alanine transaminase (may be referred to as SGPT)
AML	acute myeloid leukemia
ANA	antinuclear antibody
ANC	absolute neutrophil count
APAP	acetaminophen
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
ASPEN	American Society for Parenteral and Enteral Nutrition
AST	aspartate aminotransaminase (may be referred to as SGOT)
ATG	antithymocyte globulin
AUC	area under the curve
AV	atrioventricular
AZT	azidothymidine
BAL	British anti-Lewisite
BG	blood glucose
BID	two times daily
BLC	blood lead concentration
BMI	body mass index
BMT	bone marrow transplant
BPD	bronchopulmonary dysplasia
BPM	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAPD	continuous ambulatory peritoneal dialysis
CBC	complete blood count
CDAD	*Clostridium difficile*–associated diarrhea
CDC	Centers for Disease Control and Prevention
CDH	congenital diaphragmatic hernia
CDP-1	crystalline degradation product
CF	cystic fibrosis
CGA	calculated gestational age
CGA	comprehensive geriatric assessment
CHD	congenital heart disease
CHF	congestive heart failure
CINV	chemotherapy-induced nausea and vomiting
CLD	chronic lung disease
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
CNS	central nervous system
CPB	cardiopulmonary bypass
CPK	creatine phosphokinase
CPK-MB	creatine phosphokinase MB isoenzyme

CPR	cardiopulmonary resuscitation
CrCl	creatinine clearance
CRRT	continuous renal replacement therapy
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
CVVH	continuous venovenous hemofiltration
CYP	cytochrome P
CYP1A2	cytochrome P450 isoenzyme 1A2
CYP2A4	cytochrome P450 isoenzyme 2A4
CYP2B6	cytochrome P450 isoenzyme 2B6
CYP2C19	cytochrome P450 isoenzyme 2C19
CYP2C9/10	cytochrome P450 isoenzymes 2C9 and 2C10
CYP2E1	cytochrome P450 isoenzyme 2E1
CYP3A3/4	cytochrome P450 isoenzymes 3A3 and 3A4
DART	dexamethasone: a randomized trial
DEHP	diethylhexyl phthalate
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
DPT	Demerol, Phenergan, Thorazine
DRESS	drug reaction with eosinophilia and systemic symptoms
DVT	deep vein thrombosis
DW	dosing weight
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
ED	emergency department
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
ELBW	extremely low birth weight
EMIT	enzyme-multiplied immunoassay technique
ESA	erythropoiesis-stimulating agent
ET	endotracheal
EtOH	ethanol
EVA	ethylene vinyl acetate
FAB	digoxin immune Fab
FDA	Food and Drug Administration
FE	fat emulsion
FFP	fresh frozen plasma
FPIA	fluorescence polarization immunoassay
FT4	free thyroxine
GFR	glomerular filtration rate
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor

GVHD	graft versus host disease
H1	histamine-1 receptor antagonist
H2	histamine-2 receptor antagonist
Hb	hemoglobin; also Hgb
Hct	hematocrit
HD	hemodialysis
HHV	human herpes virus
HIB	*Haemophilus influenzae* type B
HIT	heparin-induced thrombocytopenia
HITTS	heparin-induced thrombocytopenia with thrombosis syndrome
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPLC	high-performance liquid chromatography
hr	hour
HSV	herpes simplex virus
HUS	hemolytic uremic syndrome
iNO	inhaled nitric oxide
IBW	ideal body weight
ICP	intracranial pressure
ICU	intensive care unit
IE	infective endocarditis
IgG	immunoglobulin G
IgM	immunoglobulin M
IH	idiopathic hyperphosphatasia
IM	intramuscular
INR	international normalized ratio
IO	intraosseous
IP	intraperitoneal
IQ	intelligence quotient
ISMP	Institute for Safe Medication Practices
IT	intrathecal
ITP	idiopathic thrombocytopenic purpura
IV	intravenous
IVFE	intravenous fat emulsion
IVH	intraventricular hemorrhage
IVIG	intravenous immune globulin; intravenous immunoglobulin
IVR	in vivo recovery
JIA	juvenile idiopathic arthritis
LBM	lean body mass
LD	loading dose
LDH	lactate dehydrogenase
LFT	liver function test
LGS	Lennox–Gastaut syndrome

MAC	*Mycobacterium avium* complex
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MI	myocardial infarction
MIC	minimum inhibitory concentration
min	minute
MMR	measles, mumps, and rubella
mo	month
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MTX	methotrexate
NAC	n-acetylcysteine
NAPA	n-acetylprocainamide
NEC	necrotizing enterocolitis
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
NMS	neuroleptic malignant syndrome
NMTT	n-methyl-thiotetrazole side chain
NPO	nothing by mouth
NSAID	nonsteroidal anti-inflammatory drug
OI	osteogenesis imperfecta
OTC	over-the-counter
PaO_2	arterial partial pressure of oxygen
PALS	pediatric advanced life support
PBPC	peripheral blood progenitor cell
PCA	partial-controlled analgesia
PCA	postconceptional age
PCI	percutaneous coronary intervention
PCP	phencyclidine
PDA	patent ductus arteriosus
PE	phenytoin equivalent
PID	pelvic inflammatory disease
PMA	postmenstrual age
PN	parenteral nutrition
PNA	postnatal age
PO	by mouth
PONV	postoperative nausea and vomiting
PPHN	persistent pulmonary hypertension of the newborn
PPI	proton-pump inhibitor
PRN	pro re nata; as needed
PT	prothrombin time

PTH	parathyroid hormone
PTT	partial thromboplastin time
PVC	polyvinyl chloride
PVR	pulmonary vascular resistance
q	every
RBC	red blood cell
SA	sinoatrial
SBECD	sulfobutyl ether beta-cyclodextrin sodium
SC	subcutaneous
SCr	serum creatinine
SDC	serum digitalis concentration
sec	second
SIADH	syndrome of inappropriate antidiuretic hormone
SLE	systemic lupus erythematosus
SSRI	selective serotonin reuptake inhibitor
TBW	total body weight
TCA	tricyclic antidepressant
TDD	total digitalizing dose
THC	tetrahydrocannabinol
TID	three times daily
TNA	total nutrient admixture
TNF	tumor necrosis factor
TPA	tissue plasminogen activator
TPN	total parenteral nutrition
TSH	thyroid-stimulating hormone
TTP	thrombotic thrombocytopenic purpura
UGT	uridine diphosphate–glucuronosyltransferase
UOP	urine output
USP	United States Pharmacopeia
UTI	urinary tract infection
VAD	ventricular assist device
VPA	valproic acid
Vitamin B_{12}	cyanocobalamin
VLBW	very low birth weight
VTE	venous thromboembolism
vWD	von Willebrand disease
VZV	varicella-zoster virus
WBC	white blood cell
wk	week
WGA	weeks gestational age
yr	year

Monographs

Abatacept

Brand names	Orencia
Medication error potential	Look-alike, sound-alike drug names. USP reports that Orencia may be confused with Oracea.[1]
Contraindications and warnings	**Warnings:** Concomitant use with tumor necrosis factor (TNF) antagonists or other biologic rheumatoid arthritis therapy is not recommended.[2] Hypersensitivity reactions may occur. Discontinue use if serious infection occurs. Screen for tuberculosis prior to starting therapy. Live vaccines should not be given during or until 3 months after abatacept discontinuation. Children's vaccination status should be current prior to beginning therapy.
Infusion-related cautions	An acute hypersensitivity reaction occurred in one of 190 pediatric patients treated with abatacept.[2] Appropriate medical care should be available in the event this occurs.
Dosage	**Juvenile idiopathic arthritis ≥6 years**[2,3] **<75 kg:** 10 mg/kg repeated at 2 and 4 weeks after initial infusion and q 4 wk thereafter. **75–100 kg:** 750 mg. **>100 kg:** 1000 mg. **Other uses:** One child with juvenile idiopathic arthritis-associated uveitis responded to treatment with abatacept after infliximab was discontinued due to adverse effects and etanercept and rituximab failed to elicit an improvement.[4] Seven children with juvenile idiopathic arthritis-associated uveitis refractory or intolerant to immunosuppressive and anti-TNF alpha agents demonstrated sustained improvement with abatacept therapy.[5]
Dosage adjustment in organ dysfunction	None recommended.
Maximum dosage	1000 mg.
Additives	Maltose. (See Laboratory Interference in the Comments section.)
Suitable diluents	SW to reconstitute. NS to dilute.[2]
Maximum concentration	10 mg/mL.[2]

Abatacept

Preparation and delivery	**Preparation:** Reconstitute by adding 10 mL SW with the silicone-free, disposable syringe provided. Gently rotate the vial to dissolve. Do not shake. The vial should be vented to dissipate any foam that is present.[2] The reconstituted dose must be diluted in 100 mL of NS prior to infusion. Remove the volume of the dose from the 10-mL bag of NS and then using the silicone-free syringe slowly inject the dose into 100-mL NS. Gently mix.[2] **Delivery system issues:** Infuse through a sterile, nonpyrogenic 0.2- to 1.2-micron, low protein-binding filter. **Stability:** The vial contains no preservatives and once reconstituted must be used within 24 hours.[2]
IV push	Not indicated.
Intermittent infusion	Over 30 minutes.[2]
Continuous infusion	Not indicated.
Other routes of administration	SC dosage available as a single-dose, prefilled glass syringe as 125 mg in 1 mL. This solution does not contain maltose.
Comments	**Adverse events:** Serious infections have been reported in individuals receiving TNF-alpha blocker therapy and abatacept concurrently.[2] **Laboratory interference:** Because of the maltose additive in the IV preparation, a falsely elevated blood glucose measurement may occur with some types of glucose monitors.[2] Juvenile idiopathic arthritis, juvenile rheumatoid arthritis, and juvenile chronic arthritis may be used interchangeably.

Acetaminophen Injection

Brand names	Ofirmev
Medication error potential	Calculating the dosage in milligrams (mg), but then administering the solution in milliliters (mL), has caused a 10-fold dosing error in children.[1] Look-alike, sound-alike drug names. Acetaminophen may be confused with acetazolamide.[2]
Contraindications and warnings	Past hypersensitivity to acetaminophen or any of its components.[3] Severe hepatic impairment or severe active liver disease.[3]
Infusion-related cautions	Postmarketing reports of hypersensitivity and anaphylaxis, which includes swelling of the face, mouth, and throat; respiratory distress; urticaria; rash; and pruritus.[3] Life-threatening anaphylaxis has occurred.[3]
Dosage	**Fever/pain in those unable to tolerate oral or rectal route** **Neonates (full-term):** 12.5 mg/kg q 6 hr or 15 mg/kg q 8 hr.[4] **Infants to 2 years:** 15 mg/kg q 6 hr or 12.5 mg/kg q 4 hr.[4] **2–12 years:** 15 mg/kg q 6 hr or 12.5 mg/kg q 4 hr.[3] **Adolescents and *adults* <50 kg:** 15 mg/kg q 6 hr or 12.5 mg/kg q 4 hr.[3] **Adolescents and *adults* ≥50 kg:** 1000 mg q 6 hr or 650 mg q 4 hr.[3]
Dosage adjustment in organ dysfunction	Use with caution in those with hepatic impairment.[3] Dosage adjustment may be needed if CrCl is <30 mL/min.[3] If CrCl is <10 mL/min or the patient is receiving intermittent hemodialysis or peritoneal dialysis, administer q 8 hr. No adjustment needed in continuous renal replacement therapy.[3]
Maximum dosage	15 mg/kg up to 1000 mg/dose.[3] Maximum daily dose of 75 mg/kg/day or 4 g/day.[3]
Additives	None.
Suitable diluents	Does not require further dilution[3] but can be diluted in D5W, NS, D10W, D5LR, LR, and D5NS.[3] If further diluted, stable for 1 hour.[3]
Maximum concentration	1000 mg/100 mL (10 mg/mL) with no need for further dilution.[3]
Preparation and delivery	**Stability:** Store intact vials at room temperature (20°C to 25°C). Do not refrigerate or freeze.[3] Should be used within 6 hours of accessing the vial or transferring the contents to another container.[3]
IV push	Not recommended.[3]
Intermittent infusion	Infuse over 15 minutes.[3]

Continuous infusion	Not recommended.[3]
Other routes of administration	None.
Comments	Substances that induce or regulate CYP2E1 may alter the metabolism of acetaminophen.[3] The antipyretic effects may mask fever in postsurgical patients.[3]

AcetaZOLAMIDE

Brand names	Diamox
Medication error potential	Look-alike, sound-alike drug names. ISMP reports that acetaZOLAMIDE may be confused with Diabinese.[1] USP reports that Diamox has also been confused with Aggrenox, Amoxil, Demadex, diazoxide, and Diuril.[2] USP reports that acetaZOLAMIDE has been confused with acetaminophen, acetylcysteine, and methazolamide.[2] Confusion with acetoHEXAMIDE has resulted in patient harm.[2]
Contraindications and warnings	acetaZOLAMIDE contains a sulfonamide moiety. Although rare, cross-reactivity with other sulfonamides may be associated with severe dermatological reactions (e.g., Stevens-Johnson syndrome), which have occurred due to sulfonamide structure.[3]
Infusion-related cautions	None.
Dosage	Because of limited experience with acetaZOLAMIDE, the doses and side effects have not been established. No pediatric-specific problems have been documented to date. **Acute glaucoma:** 20–40 mg/kg/day divided q 6 hr (not to exceed 1 g/day).[4] **Edema/diuresis/urinary alkalinization:** 5 mg/kg/dose[4,5] or 150 mg/m^2[4,5] once daily as required to achieve forced alkaline diuresis. (See Comments section.) **Epilepsy (various types):** 8–30 mg/kg/day in divided doses (in *adults,* 375–1000 mg daily).[3] **Posthemorrhagic ventricular dilatation:** Studies have shown increased rates of shunt placement and greater neurological morbidity or nephrocalcinosis with maximum tolerable doses (100 mg/kg/day); therefore, use of acetaZOLAMIDE is not recommended.[6–8] **Pseudotumor cerebri:** 40–120 mg/kg/day divided q 6–8 hr up to 2 g/day.[9]
Dosage adjustment in organ dysfunction	Not effective at CrCl <20 mL/min.[10] If CrCl is 20–50 mL/min, give q 12 hr.[11] Avoid if CrCl <10 mL/min.[11] Should not be used in hepatic cirrhosis due to the risk of encephalopathy.[3]
Maximum dosage	100 mg/kg/day[12] up to 1–2 g/day.[4,9]
Additives	2.049 mEq of sodium/500 mg acetaZOLAMIDE.[13]
Suitable diluents	D2.5W, D5W, D10W, NS, LR, or R.[13]
Maximum concentration	100 mg/mL.[3,13]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.
IV push	100 mg/mL at a rate not to exceed 500 mg/min.[4]

Intermittent infusion	100 mg/mL.[3,13]
Continuous infusion	Not administered by this method.
Other routes of administration	IM administration not recommended[3]; very painful due to alkaline pH of approximately 9.6.[13]
Comments	**Rare adverse effects:** acetaZOLAMIDE is a carbonic anhydrase inhibitor that shares the pharmacological actions and toxic potentials of this class of medications.[3] May cause hypokalemia, paresthesias, and kidney stones.[3] Overdoses or too frequent dosage may cause a failure to produce diuresis. acetaZOLAMIDE should be withheld for 1–2 days to allow for kidney recovery.[3] **Laboratory interference:** May cause false–positive results for urinary protein with Albustix, Labstix, Albutest, Bumintest; interferes with high-performance liquid chromatography method for assaying theophylline and serum uric acid.[4]

Acetylcysteine (NAC)

Brand names	Acetadote
Medication error potential	Look-alike, sound-alike drug names. Acetylcysteine (NAC) may be confused with Mucomyst and Mucinex.[1]
Contraindications and warnings	**Warnings:** Caution in patients with asthma or history of bronchospasm. Acute flushing and erythema can occur 30–60 minutes after initiation of the infusion, often with spontaneous resolution despite continued infusion.[2]
Infusion-related cautions	Anaphylactoid reactions and death have been reported[2] and some recommend infusing the loading dose over 60 minutes.[3] Once the anaphylactoid reaction has been treated (e.g., antihistamines, H_2 blockers, and in severe cases epinephrine), NAC can be reinstituted cautiously, but it should be discontinued if anaphylactoid reaction recurs.[2]
Dosage	**Acetaminophen overdose*:** Serum acetaminophen concentrations that are obtained within 4 hours of ingestion are not predictive of severity.[2] Likewise, undetectable serum concentrations, in a patient who delayed seeking medical care, may not reflect the ingestion of a potentially lethal dose.[2] In addition, with an extended-release acetaminophen preparation, an acetaminophen level drawn within 8 hours of the ingestion may be misleading, and a second level should be drawn 4–6 hours after the initial level.[2] Use the Rumack-Matthew nomogram** to estimate the potential for hepatotoxicity due to acetaminophen overdose and to guide therapy with NAC. Ideally, it should be administered within 8 hours of acetaminophen ingestion to prevent or lessen hepatic injury; however, it may be effective when given 24 hours or longer after ingestion. * Despite low or undetectable acetaminophen serum concentrations, NAC should be given if any signs of hepatotoxicity are evident.[2] ** The nomogram is less predictive in a chronic ingestion or in an overdose with an extended release product. The nomogram also does not take into account patients at high risk of acetaminophen toxicity (e.g., alcoholics, malnourished patients) or individuals ingesting larger than recommended acetaminophen doses for extended periods of time.[2] Infuse loading dose of 150 mg/kg over 60 minutes, followed by 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours (for a full course consisting of 300 mg/kg administered IV over 20.25 hours).[2] (See Comments section.) One report suggests that standard acetaminophen overdose protocols may not be adequate in cases of massive acetamiophen ingestion.[4] **Modified acetaminophen overdose regimens:** Some studies report alternative NAC dosing regimens. One retrospective study reported using a standard preparation of IV NAC (30 g in 1 L of D5W) with a loading dose of 150 mg/kg administered over 60 minutes followed by a continuous infusion of 14 mg/kg/hr for 20 hours.[5] Another study reported the use of NAC (using D5½NS) with a bolus of 150 mg/kg over 60 minutes followed by a continuous infusion of 10 mg/kg/hr for 20 hours.[6] The ½NS was added to prevent hyponatremia that has been reported with standard IV dosing.[6,7] **Advanced cerebral adrenoleukodystrophy:** Administration of NAC (140 mg/kg/day IV followed by 70 mg/kg *orally* 4 times a day) before (54–67 days) and after (114–250 days) hematopoietic stem cell transplant was noted to protect from fulminant demyelination in three children.[8]

Dosage *(cont.)*

Prevention of acute renal failure associated with nephrotoxic agents: *Adult* studies have reported that both oral[9,10] and IV[10] dosing of NAC, in addition to appropriate hydration, can prevent renal dysfunction induced by radiographic contrast agents, but there are no pediatric studies with dosing recommendations. One pediatric study reported two patient cases in which NAC attenuated ifosfamide-induced acute renal failure. One patient received IV NAC (loading dose of 150 mg/kg over 60 minutes, followed by 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours) and the other was given oral NAC (600 mg BID).[11]

Prevention of acute kidney injury after cardiopulmonary bypass: Several *adult* studies have reported no difference in prevention of acute kidney injury after cardiopulomonary bypass in patients receiving NAC compared to those receiving placebo.[12–16] But one pediatric study including 21 neonates reported an improvement in urine output, time to negative fluid balance, and attenuation of rise in SCr after an IV bolus of NAC (100 mg/kg in D5W) followed by an infusion of NAC (10 mg/kg/hr) for 24 hours after separation from cardiopulmonary bypass.[17]

Prevention of bronchopulmonary dysplasia (BPD): When compared to placebo, there was no difference in the development of BPD or death in 194 infants (500–999 g) who received a 6-day continuous infusion of NAC (16–32 mg/kg/day beginning within 36 hours of birth).[18]

Nonacetaminophen-induced hepatic disease: NAC reduced liver biochemistries and serum ferritin in three children with TPN-associated liver disease. Each was begun on estimated maintenance requirements of cysteine (20–50 mg/kg/day of NAC). The NAC dose was increased by 10 mg/kg/day q 1–2 mo to maximum doses of 70, 120, and 135 mg/kg/day. Doses were infused over 12 hours and continued for 3–18 months. The improvements in liver function occurred with larger NAC dosages.[19]

A prospective, randomized study including children and *adults* (1–64 years of age) with early liver toxicity due to allogenic hematopoietic stem cell transplantation reported that the introduction of NAC at the first sign of liver toxicity did not prevent progression of liver disease.[20]

A retrospective review including 170 children with nonacetaminophen-induced acute liver failure compared standard of care (n = 59) and standard of care plus NAC (n = 111). NAC, given as continuous infusion of 100 mg/kg/day for a median of 5 days (range 1–77 days), was safe and associated with shorter length of hospital stay, higher incidence of native liver recovery without transplantation, and better survival after transplantation compared to the historical standard of care.[21] These findings are consistent with the *adult* literature.[22]

Dosage adjustment in organ dysfunction

Despite a threefold increase in NAC plasma concentrations in patients with hepatic cirrhosis, there are no recommendations for reduction of NAC dosing in patients with hepatic impairment.[2] No data are available to determine if dosage adjustment is needed for moderate or severe renal impairment.[2] Some suggest a 25% reduction in maintenance dose when the CrCl is $<$10 mL/min.[23]

Maximum dosage

Cummulative dose of 300 mg/kg per treatment course.[2] No adverse effects were noted following a mean rate of 4.2 mg/kg/hr for 24 hours in 10 preterm infants (gestational age: 25–31 weeks; weight: 500–1380 g) or following infusion of 0.1–1.3 mg/kg/day for 6 days in six neonates (gestational age: 26–30 weeks; weight: 520–1335 g).[24] Also, in a study including 194 infants (weight: 500–999 g) receiving NAC at a constant infusion rate of 16–32 mg/kg/day for 6 days, no adverse effects were observed that could be attributed to NAC.[18]

Additives

Disodium edetate,[25] and sodium hydroxide[2,25] (used for pH adjustment).[2] Reported pH of 6–7.5 and[2,25] osmolality of 2600 mOsm/L.[2]

Acetylcysteine (NAC)

Suitable diluents

D5W, ½NS, and SW.[2,3]

Maximum concentration

Up to 50 mg/mL for loading dose and 10 mg/mL for maintenance dose. Adjust total volume as needed for patients' weight and those requiring fluid restriction.[2]

Weight (kg)	Loading Dose (150 mg/kg over 60 min)		2nd Dose (50 mg/kg over 4 hr)		3rd Dose (100 mg/kg over 16 hr)	
	Acetadote (mL)	Diluent (mL)	Acetadote (mL)	Diluent (mL)	Acetadote (mL)	Diluent (mL)
10	7.5	30	2.5	70	5	140
15	11.25	45	3.75	105	7.5	210
20	15	60	5	140	10	280
25	18.75	100	6.25	250	12.5	500
30	22.5	100	7.5	250	15	500
40	30	200	10	500	20	1000
50	37.5		12.5		25	
60	45		15		30	
70	52.5		17.5		35	
80	60		20		40	
90	67.5		22.5		45	
100	75		25		50	

Preparation and delivery

Delivery system issues: Contact with rubber, copper, iron, and cork may inactivate NAC.[3]

Stability: Stable 24 hours after dilution at room temperature. Although solution may turn from colorless to slight pink or light purple color following puncture of stopper, this does not affect the activity of NAC.[2]

IV push

Not administered by this method.

Intermittent infusion

Loading dose should be given over 60 minutes to reduce the potential for a life-threatening anaphylactoid reaction, but one study reports the safe use of a 15-minute infusion rate in patients between 15 and 83 years of age.[3] (See Infusion-Related Cautions section.)

Continuous infusion

First (50 mg/kg) and second (100 mg/kg) maintenance doses should be given over 4 hours and 16 hours, respectively.[2,3] Infusions of 0.8–5.6 mg/kg/hr have been used safely in newborns.[19]

Other routes of administration

None.

Comments

Adverse reactions: One study reported the incidence of adverse drug reactions in patients receiving NAC for acetaminophen toxicity. Adverse reactions were observed in 67.6% of patients. There was a significant association between low serum acetaminophen concentrations and NAC-associated cutaneous anaphylactic reactions (but no other reported adverse events).[26] Another report noted that delayed time to initiation of NAC was a risk factor for developing anaphylactic reactions, suggesting early NAC infusion may be protective against this type of event.[27]

Other: Contact a poison center at 1-800-222-1222 to obtain information about the clinical management of acetaminophen overdoses.

NAC crossed the placenta when a mother was treated following an acetaminophen exposure.[28]

A study comparing the 20-hour IV NAC and the 72-hour *oral* NAC protocols for acetaminophen overdose favored the IV protocol in patients presenting early (within 12 hours of ingestion) and the *oral* protocol in patients presenting late (greater than 18 hours after ingestion) with respect to the risk of hepatotoxicity.[29]

Acyclovir Sodium

Brand names	Generic
Medication error potential	USP reports that acyclovir has been confused with Retrovir, valacyclovir, and ganciclovir, and that Zovirax has been confused with Zyvox, Zostrix, Valtrex, Zithromax, and Zyloprim.[1] ISMP reports that Zovirax has been confused with Doribax, Zyvox, and Zostrix.[2]
Contraindications and warnings	**Contraindications:** Hypersensitivity to acyclovir or valacyclovir.[3] **Warnings:** Renal failure and thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS) have both been reported with acyclovir. Deaths have occurred due to renal failure and TTP/HUS. Acyclovir should be used with caution in patients with underlying neurological abnormalities, as well as those with serious renal, hepatic, or electrolyte abnormalities or significant hypoxia.[3]
Infusion-related cautions	To decrease the risk of nephrotoxicity, the patient should be adequately hydrated before and during the infusion.[3,4] Extravasation may cause inflammation and phlebitis at the injection site.[3,5] See Appendix E for additional information regarding extravasation treatment.
Dosage	Doses generally range from 15–60 mg/kg/day or 1500 mg/m^2/day divided q 8 hr depending on the infection.[3,6–13] Obese patients should be dosed using ideal body weight.[3] **Herpes simplex virus (HSV)** **Neonatal HSV:** 30–60 mg/kg/day divided q 8 hr for 10–21 days.[3,7,12,13] **HSV encephalitis** **≥3 months–12 years:** 60 mg/kg/day divided q 8 hr for 10–21 days; some experts recommend 45 mg/kg/day divided q 8 hr for 14–21 days.[3,12,13] **≥12 years:** 30 mg/kg/day divided q 8 hr for 10–21 days.[3,12] **Genital HSV (severe cases), ≥12 years:** 15 mg/kg/day divided q 8 hr for 5–7 days.[12] **HSV in immunocompromised host (localized, progressive, or disseminated)** **<12 years:** 30 mg/kg/day divided q 8 hr for 7–14 days.[12] **≥12 years:** 15 mg/kg/day divided q 8 hr for 7–14 days.[12] **HSV-seropositive patients:** 15 mg/kg/day divided q 8 hr during risk period.[12] **Varicella-zoster virus (VZV)** **Primary** **Immunocompetent hosts >2 years:** 30 mg/kg/day divided q 8 hr or 1500 mg/m^2/day divided q 8 hr for 7–10 days.[12] **Immunocompromised hosts** **<12 years:** 60 mg/kg/day divided q 8 hr for 7 days.[3] **>12 years:** 30 mg/kg/day divided q 8 hr for 7 days.[3] **or** **<1 year:** 30 mg/kg/day divided q 8 hr for 7–10 days.[12] **≥1 year:** 1500 mg/m^2/day (or 30 mg/kg/day) divided q 8 hr for 7–10 days.[9,11,12]

Dosage *(cont.)*

Initiate therapy as soon as possible after rash appears. Early initiation therapy (<24–72 hours) is associated with more rapid improvement and less dissemination than late initiation therapy (>3–5 days).[9]

IV therapy is recommended for the duration of treatment in immunocompromised hosts.[12]

Sixty-six pediatric renal transplant recipients with VZV were given 1500 mg/m^2/day divided q 8 hr. Azathioprine was temporarily discontinued until the lesions crusted over and no new lesions appeared; at that time, azathioprine was restarted at the usual dose. Three recipients experienced acute rejection that responded to prednisone. One patient died.[14]

Zoster

Zoster in immunocompetent host, all ages: Same as dosing for varicella in immunocompromised host.[12]

Zoster in immunocompromised host, all ages: 30 mg/kg/day divided q 8 hr for 7–10 days.[12]

Prevention or suppression of cytomegalovirus infection in allogeneic bone marrow transplant recipients (this use has largely been replaced by ganciclovir): 1500 mg/m^2/day divided q 8 hr beginning 5 days before transplantation and continuing 30 days after.[8, 15]

Aplastic anemia (use not established): 15 mg/kg/day (schedule not provided) for 10 days has been given to two patients (one, a 13-year-old girl) who had severe, possibly viral related, aplastic anemia refractory to standard treatment.[6]

Dosage adjustment in organ dysfunction

Adjust dosage in patients with renal dysfunction.[3,12,16–18] If CrCl is 25–50 mL/min, give normal dose q 12 hr; if CrCl is 10–25 mL/min, give normal dose q 24 hr, and if CrCl is <10 mL/min, give 50% of the dose q 24 hr.[3]

Another source recommends the following dose adjustment based on GFR[18]:

GFR (mL/min/1.73m^2)	Dose
30–50	10 mg/kg q 12 hr
10–29	10 mg/kg q 24 hr
<10	5 mg/kg q 24 hr

Neonates with hepatic or renal dysfunction and young premature infants may also require dose adjustment.[17]

Maximum dosage

Do not exceed 20 mg/kg q 8 hr.[3]

An 11-day-old neonate has received 258 mg/kg of IV acyclovir in a 24-hour period that was treated with NS hydration; the patient experienced only a transient increase in SCr.[19]

Additives

Contains 49 mg sodium/500 mg acyclovir.[3]

Suitable diluents

D5W, NS, D5NS, LR.[20]

Maximum concentration

≤7 mg/mL.[3,20] Infusion of a solution ≥10 mg/mL increases the risk of phlebitis and extravasation.[3,21]

Acyclovir Sodium

Preparation and delivery	**Stability:** Vials should be reconstituted with SW for injection and should be used within 12 hours. Once diluted for administration, doses should be used within 24 hours.[3,20] Refrigeration may cause precipitation; however, the precipitate redissolves at room temperature and potency does not appear to be affected.[3,20] BW for injection containing parabens or benzyl alcohol should not be used to dilute acyclovir sodium powder because precipitation could occur.[3,20] **Compatibility:** For PN compatibility information, please see Appendix D.
IV push	Not recommended.[3] Rapid administration (<10 minutes) can cause crystalluria, elevations in serum urea and SCr, renal tubular damage, and acute renal failure.[3,4]
Intermittent infusion	The dose should be infused over 1 hour to minimize renal dysfunction.[3,4,20]
Continuous infusion	No information available to support administration by this method.
Other routes of administration	Not recommended.[3,20]
Comments	**Significant adverse drug effects:** Nonherpetic vesicular eruptions occurred in a child receiving acyclovir for presumed herpes simplex encephalitis.[22] **Drug interactions:** Coadministration with probenecid has been shown to increase the mean half-life and the area-under-the-concentration time curve for acyclovir.[3] Consult appropriate resources for dosing recommendations before combining probenecid with acyclovir. **Pharmacokinetic considerations:** A pharmacokinetic study of IV acyclovir (15 mg/kg/day) in patients 9 months to 20 years of age with malignancy showed that those with good renal function and/or lower body weight could possibly be underdosed.[23] **Other:** A 28-week premature infant has been successfully treated with IV acyclovir for 21 days after the mother presented with eczema herpeticum at the time of delivery.[24]

Adalimumab

Brand names	Humira
Medication error potential	Look-alike, sound-alike drug names.[1] Humira may be confused with Humulin or Humalog. Humira Pen may be confused with HumaPen Memoir.
Contraindications and warnings	**U.S. boxed warnings** **Risk of serious infections:** Patients receiving adalimumab are at risk for developing serious infections, including tuberculosis, bacterial sepsis, invasive fungal infections and other opportunistic infections. Those with active infections should not begin treatment. Discontinue therapy in those who develop serious infection or sepsis while on treatment.[2] Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test. If the skin test is positive, treatment of tuberculosis should be started prior to beginning treatment with adalimumab.[2] (See Comments section.) **Hepatosplenic T-cell lymphomas:** These have been reported in adolescents and young *adults* with inflammatory bowel disease treated with tumor necrosis factor (TNF) blockers, including adalimumab.[2] **Lymphoma and other malignancies:** There is a increased risk of lymphoma and other cancers in children and adolescents treated with TNF blockers, including adalimumab.[2] **Other warnings:** Anaphylaxis has been reported.[2] Appropriate medical care should be available in the event this occurs. Hepatitis B carriers should be monitored during and several months after completing therapy, due to the risk of reactivation of hepatitis B. If reactivation occurs, stop therapy and begin antiviral treatment.[2] The needle cover of the prefilled syringes contains latex. Those with latex allergy should not handle the syringes.[2,3]
Infusion-related cautions	None reported.
Dosage	**Juvenile idiopathic arthritis, 4–17 years**[2–4] **15 kg to >30 kg:** 20 mg SC every other week. **≥30 kg:** 40 mg SC every other week. **Crohn disease/ulcerative colitis, 9–18 years**[5-7] **Induction** **<40 kg:** 80 mg followed by 40 mg on week 2. **≥40 kg:** 160 mg followed by 80 mg on week 2. **Maintenance (start on week 4 [2 weeks after induction])** **<40 kg:** 20 mg every other week. **≥40 kg:** 40 mg every other week. **Uveitis, >4 years**[8-11] **BSA dosing:** 24 mg/m^2 q 2 wk.

Adalimumab

Dosage *(cont.)*	**Weight-based dosing** **<30 kg:** 20 mg every other week. **≥30 kg:** 40 mg every other week. ***Adults:*** Adalimumab is used to treat rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn disease, and plaque psoriasis in *adults*.[2,3]
Dosage adjustment in organ dysfunction	None reported.[2]
Maximum dosage	40 mg as a single injection. Higher doses may require multiple injections.
Additives	None.
Suitable diluents	Not diluted.
Maximum concentration	50 mg/mL (commercially available).
Preparation and delivery	Available as disposable prefilled syringes (20 mg/0.4 mL, 40 mg/0.8 mL) or as a prefilled injection pen (40 mg/0.8 mL). Must be refrigerated until use.[2,3] **Photosensitivity:** Protect from light exposure until ready to use.
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	Not indicated.
Other routes of administration	Administer by SC injection.[2,3]
Comments	A negative skin test for tuberculosis does not rule out the possibility of disease since patients with immune diseases may exhibit cutaneous anergy.[12] **Drug interactions:** An increased incidence of infection has been noted when used with anakinra or abatacept.[2,3] Live vaccines should not be given with adalimumab.[2,3] Methotrexate decreases clearance; however, no change in adalimumab dosage is recommended.[2]

Adenosine

Brand names	Adenocard, Adenoscan
Medication error potential	High-alert medication (anti-arrhythmic) that has an increased risk of causing significant patient harm if it is used in error.
Contraindications and warnings	**Contraindications:** Known hypersensitivity to adenosine.[2] Adenosine should not be given in second- or third-degree atrioventricular (AV) block or sinus node disease (e.g., sick sinus syndrome, symptomatic bradycardia), unless a functioning artificial pacemaker is placed.[2] Adenosine should also not be used in patients with Wolff-Parkinson-White syndrome or wide complex tachycardia.[3] Although not listed in the prescribing information, some suggest that adenosine should be contraindicated in heart transplant recipients as adenosine may cause prolonged asystole.[4] **Warnings** **Arrhythmias, postconversion:** A variety of new rhythms (e.g., premature ventricular contractions, atrial premature contractions, sinus bradycardia, sinus tachycardia, skipped beats, and varying degrees of AV nodal block) may appear on the ECG at the time of conversion to normal sinus rhythm; however, these generally last only a few seconds and resolve without intervention.[2] **Bronchoconstriction:** Patients with a history of reactive airway disease may experience bronchospasm and respiratory failure.[2,5–7] Aminophylline has been used to relieve bronchospasm associated with adenosine.[7] **Heart block:** Adenosine decreases conduction through the AV node and may produce first-, second-, or third-degree heart block, which is generally self-limiting due to adenosine's short half-life.[2] Additional doses should not be given if high-level block develops after one dose.[2] Transient or prolonged episodes of asystole have been fatal. Rarely, ventricular fibrillation has been reported following adenosine administration, including both resuscitated and fatal events.[2] (See Comments section.)
Infusion-related cautions	None.
Dosage	**Pulmonary hypertension:** 50 mcg/kg/min has been associated with improved PaO_2,[8–10] decreased pulmonary arterial pressure,[9] and rapid weaning of oxygen, ventilator support, and nitric oxide[10] in some neonates and infants with persistent pulmonary hypertension. One patient experienced hypotension when the dose was increased to 80 mcg/kg/min, but blood pressure corrected after the dose was decreased to 50 mcg/kg/min.[9] No other reports of tachycardia or hypotension were noted.[8–10] **Stress test in aortic valve disease or Kawasaki disease:** 0.14 mg/kg/min for 6 minutes.[11] **Supraventricular tachycardia** **Initial dosing:** 0.05[2–4,12] to 0.1[2–4,12–18] mg/kg. Infuse over 1–2 seconds, then immediately flush catheter with saline.[2,12] One report noted that only 9% of infants responded to a dose of 0.05 mg/kg and the median effective dose was 0.15 mg/kg.[13] The maximum single initial dose is 0.3 mg/kg in neonates, 0.5 mg/kg in children[19] and 6 mg in *adults*.[3,12] One report suggests a larger initial dose of 0.2–0.25 mg/kg in both infants and children may reduce the risk of unsuccessful cardioversion by 35%.[20] **Subsequent dosing:** If conversion does not occur in 1–2 minutes, increase dose by 0.05–0.1 mg/kg.[2,12] Follow each bolus with a saline flush. This process should continue until sinus rhythm is established or a maximum single dose of 0.3 mg/kg (maximum of 12 mg) is used.[2]

Dosage *(cont.)*	**Pretreatment in children undergoing cardiac surgery (prevention of ischemia and reperfusion injury):** Adenosine was infused through a central venous catheter at 0.05 mg/kg/min for the first minute, then increased by 0.05 mg/kg/min each minute up to 0.35 mg/kg/min (maximum dose maintained for 4 additional minutes). The total dose of adenosine was 2.45 mg/kg. There was a 5-minute interval between the completion of adenosine and initiation of cardiac bypass surgery.[21]
Dosage adjustment in organ dysfunction	No dosage adjustment necessary in renal dysfunction.[22]
Maximum dosage	The maximum single dose is 0.3 mg/kg in neonates, 0.5 mg/kg in children,[19] and up to 12 mg in *adults*.[2,3] A preterm neonate receiving theophylline required doses of 0.4–0.8 mg/kg to convert to normal sinus rhythm.[23] Over a 14.5-hour period, a 3-week-old was given 119 doses of 0.1–0.2 mg/kg.[24] A 14-year-old adolescent who failed to respond to an 18-mg dose was believed to have ventricular tachycardia.[18] (See Comments section.)
Additives	9 mg/mL of sodium.[25]
Suitable diluents	D5W, NS, LR, and D5LR.[25]
Maximum concentration	3 mg/mL (available commercially).[2]
Preparation and delivery	**Stability:** Store at room temperature. Do not refrigerate as crystallization may occur. Crystals may be dissolved by warming to room temperature. The solution must be clear at the time of use.[25]
IV push	Over 1–2 seconds, followed by a rapid saline flush.[2,3,25]
Intermittent infusion	Not given via this method.
Continuous infusion	Nine infants received a continuous infusion of adenosine (3 mg/mL in NS).[8] Another child received a continuous infusion, but the concentration and solution type were not provided.[26]
Other routes of administration	IO in emergencies,[3,12,27] but one case series reported inability to successfully convert the arrhythmia following administration by this method.[27]
Comments	**Rare adverse effects:** Transient flushing, dyspnea, headache, complete AV block, sinus bradycardia, and other rhythm disorders have been reported.[2,3] **Drug interactions:** Although no causal relationship or drug–drug interaction has been established, adenosine should be used cautiously in patients receiving digoxin and less frequently with digoxin and verapamil since ventricular fibrillation, including resuscitated and fatal events, have occurred.[2] Adenosine effects are antagonized by methylxanthines (e.g., theophylline, caffeine); hence, a larger dose of adenosine may be required.[2] The effects of adenosine are potentiated by dipyridamole. Thus, smaller doses of adenosine may be effective in the presence of dipyridamole.[28] Because adenosine decreases conduction through the AV node, higher degrees of heart block may be produced in the presence of carbamazepine.[2,3]

Albumin (Normal Human Serum)

Brand names	**50 mg/mL:** Albuked 5, Albuminar-5, AlbuRx 5, Albumin (Human) 5% Solution, Albutein 5%, Buminate 5%, Plasbumin-5 **200 mg/mL:** Albuminar, Human Albumin Grifols 20%, Plasbumin-20 **250 mg/mL:** Albuked, Albuminar-25, Albumin (Human) 25% Solution, Albutein 25%, AlbuRx 25, Buminate 25%, Flexbumin 25%, Human Albumin Grifols 25%, Kedbumin, Plasbumin-25
Medication error potential	None noted.
Contraindications and warnings	**Contraindications**[1]**:** Patients who (1) are severely anemic, (2) have congestive heart failure (CHF) with normal or increased intravascular volume, and (3) have known hypersensitivity to albumin products. Anaphylaxis has been reported in an *adult*.[2]
Infusion-related cautions	Too rapid infusion may result in acute hypertension or vascular overload, causing pulmonary edema or cardiac failure.[1] Infusion over a longer time decreases the risk for the development of CHF.[3] Premature neonates are at risk for intraventricular hemorrhage from rapid intravascular volume expansion.[4] Allergic reactions may result in chills, fever, nausea, vomiting, or urticaria.[1]
Dosage	**Hypovolemia:** 0.5–1 g/kg.[1] 20 mL/kg of 4.5% (0.9 g/kg)[5] and 5% albumin (1 g/kg)[6] have been given over 20 minutes in premature neonates. A post hoc analysis of an *adult* randomized controlled trial found that NS was preferable to albumin 4% for acute resuscitation of patients with severe traumatic brain injury (improved mortality and neurologic outcomes).[7] **Hypoalbuminemia:** Albumin deficits have been replaced by intermittent infusions of up to 1 g/kg of albumin 25%[8]; however, the continuous infusion of albumin results in a more sustained increase in serum albumin concentration.[9] The albumin deficit can be estimated with the following equation: g albumin = weight (kg) × 3 dL/kg × (3.5 – observed serum albumin in g/dL)[10,11] **Nephrotic syndrome (controversial):** 0.25–1 g/kg of albumin 25% infused over ≥1–12 hours.[3,12,13] Furosemide (0.5–2 mg/kg)[3,12–14] infusions may accompany or follow the albumin infusion and have been shown to result in better weight loss, diuresis, and sodium excretion compared to either therapy alone.[14,15] Alternatively, 1 g/kg of albumin 20% over 4 hours with furosemide continuous infusion of 0.3 mg/kg/hr has also been used.[15] **Neonatal hyperbilirubinemia:** In one randomized study, neonates receiving 1 g/kg of albumin 20% 1 hour before exchange transfusion had a greater reduction in total serum bilirubin and required a shorter duration of phototherapy compared to those receiving exchange transfusions without albumin.[16]
Dosage adjustment in organ dysfunction	None noted.[1]
Maximum dosage	125 g in 24 hours or 250 g in 48 hours have been given to *adults*.[1,3]

Albumin (Normal Human Serum)

Additives	Contains 130–160 mEq sodium/L of albumin.[1,17] Aluminum is present as a contaminant. Formulations containing ≤200 mcg/L aluminum include AlbuRx 5, AlbuRx 25, Albutein 5%, Albutein 25%, Human Albumin Grifols 20%, Human Albumin Grifols 25%, Kedbumin, Plasbumin-5, and Plasbumin-25.[18–26] Contains no preservatives or antimicrobials.[1,17]
Suitable diluents	D5W, D10W, or NS.[1,17] In patients who require sodium restriction, a 5% albumin solution that contains less sodium can be prepared by diluting each 1 mL of albumin 25% in 4 mL of D5W or D10W. However, infusion of large amounts of albumin diluted with D5W can result in hyponatremia; therefore, when using large volumes of albumin, dilution in NS is preferred.[1,17] Renal failure and fatal hemolysis may occur if SW is used as a diluent.[1,17,27,28]
Maximum concentration	Undiluted.
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information. **Delivery:** Do not use if solution is turbid.[1] The infusion should begin within 4 hours of opening the bottle.[1,17] Institution-specific protocols for blood product infusions should be used to guide infusion duration from an opened bottle. Solutions containing >25 g/L of albumin are more likely to occlude 0.22-micron inline filters; however, PN solutions containing as little as 10.8 g/L caused filter occlusion.[29,30]
IV push	When used as a plasma volume expander in the treatment of hypovolemic shock, the rate of administration should be adapted to the patient response.[1] (See Infusion-Related Cautions section.)
Intermittent infusion	Infuse over 30–60 minutes. In severe hypovolemia, faster rates may be required.[1] (See Infusion-Related Cautions section.)
Continuous infusion	Can be infused continuously. (See Preparation and Delivery section.)
Other routes of administration	Not indicated.
Comments	**Other:** Albumin is derived from pooled human plasma that has the theoretical potential to contain infectious agents including the causative agent for Creutzfeldt-Jakob disease and West Nile virus. Donor screening has greatly decreased the risk for transmission of hepatitis B, hepatitis C, and HIV.[31]

Alfentanil

Brand names	Alfenta, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that alfentanil has been confused with SUFentanil; no patient harm resulted.[2] Alfentanil may also be confused with Anafranil, fentaNYL, or remifentanil.[3]
Contraindications and warnings	**Contraindications:** Alfentanil is contraindicated in patients with a hypersensitivity to the drug or known intolerance to opioid agonists.[4] **Warnings:** Alfentanil should only be administered by persons specifically trained in the use of IV anesthetics.[4]
Infusion-related cautions	Significant bradycardia, muscle or chest wall rigidity (dose-related), and apnea may occur early in administration of alfentanil or following rapid administration.[4,5] Pretreatment with atropine and a nondepolarizing neuromuscular blocking agent may aid in minimizing these adverse effects. Ventilatory support is indicated.[4] An opioid antagonist, resuscitation and intubation equipment and oxygen should be readily available when using alfentanil.[4]
Dosage	*Alfentanil is not recommended in children <12 years.*[4] Dosages vary depending on the desired degree of analgesia/anesthesia and adjunctive therapies (e.g., halothane, propofol). **Dosing adjustment for obesity:** When dosing obese (>20% above ideal body weight) patients, use lean body weight.[4] (See Appendix B.) **Anesthesia (children >12 years and *adults*)**[4,6] **Incremental injection of short duration (≤30 minutes)** **Spontaneously breathing or assisted ventilation when required:** Induction 8–20 mcg/kg; maintenance 3–5 mcg/kg q 5–20 min or 0.5–1 mcg/kg/min (total dose 8–40 mcg/kg). **Laryngoscopy and intubation (assisted or controlled ventilation required):** Induction 20–50 mcg/kg; maintenance 5–15 mcg/kg q 5–20 min (total dose up to 75 mcg/kg). **Continuous infusion (>45 minutes)** **To attenuate response to intubation and incision (assisted or controlled ventilation required):** Induction 50–75 mcg/kg; maintenance 0.5–3 (average 1–1.5) mcg/kg/min; titrate to desired effect; total dose dependent on procedure. **Anesthetic induction (>45 minutes)** **Assisted or controlled ventilation required:** Induction 130–245 mcg/kg; maintenance 0.5–1.5 mcg/kg/min or general anesthetic; total dose dependent on procedure (administer slowly over 3 minutes; concentration of inhalation agents should be decreased by 30% to 50% for first hour). **Monitored anesthesia care (MAC)** **For sedated and responsive, spontaneously breathing patients:** Induction 3–8 mcg/kg; maintenance 3–5 mcg/kg q 5–20 min or 0.25–1 mcg/kg/min (total dose 3–40 mcg/kg).

Dosage *(cont.)*	**The following doses have been reported in children <12 years:** **Neonates (preterm and term) and infants** **Sedation/analgesia during mechanical ventilation:** 9–25 mcg/kg over 0.5–1 minute[5,7] or 15–20 mcg/kg over 30 minutes followed by an infusion of 3–5 mcg/kg/hr.[8] **Anesthesia:** 20 mcg/kg to facilitate intubation[9]; 25 mcg/kg alone, or 12 mcg/kg with regional nerve block to provide analgesia during abdominal or genitourinary surgery.[10] **Children (<12 years)** **Sedation/analgesia in spontaneously breathing patients:** 20 mcg/kg along with propofol was given to 20 patients for lumbar punctures. Supplemental oxygen was required in 50% of patients.[11] **Anesthesia:** Induction 10–100 mcg/kg (12.5–25 mcg/kg when combined with halothane)[12–17]; maintenance 2.5–5 mcg/kg/min.[13] Analgesia during surgery: 25 mcg/kg alone or 12 mcg/kg with regional nerve block to provide analgesia during abdominal or genitourinary surgery.[10] **Infants and children on cardiac bypass (congenital heart repair):** 20 mcg/kg for induction followed by continuous infusion of 1 mcg/kg/min with supplemental doses of 5 mcg/kg PRN.[18]
Dosage adjustment in organ dysfunction	No dosage adjustment required in patients with renal dysfunction.[19] Patients with hepatic dysfunction may require smaller doses to achieve the same therapeutic effect.[4] Average doses may lead to medication accumulation; therefore, caution is warranted on administration of alfentanil to patients with liver dysfunction.[4]
Maximum dosage	Dosages are titrated to the desired level of sedation or analgesia.[4]
Additives	None.
Suitable diluents	D5W, D5NS, NS, LR.[20]
Maximum concentration	80 mcg/mL.[20]
Preparation and delivery	Dilute prior to administration.[4,20]
IV push	≤80 mcg/mL over 3–5 minutes.[4,20] Doses ≤100 mcg/kg have been given over 30 seconds.[13,17] (See Infusion-Related Cautions section.)
Intermittent infusion	25–80 mcg/mL over 30 minutes.[8,20]
Continuous infusion	25–80 mcg/mL at a rate ≤5 mcg/kg/min.[4,8,12,13] (See Dosage section.) After the first hour, rates may need to be decreased by 30% to 50% in some patients.[4]

Alfentanil

Other routes of administration	No information available to support administration by other routes.
Comments	**Significant adverse effects:** Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias, and hypotension have been reported with alfentanil use.[4] Epileptiform activity has occurred in patients receiving alfentanil during epilepsy surgery.[21,22]

Allopurinol Sodium

Brand names	Aloprim
Medication error potential	Look-alike, sound-alike drug names. USP reports that allopurinol has been confused with atenolol and enalapril. No patient harm resulted.[1]
Contraindications and warnings	**Contraindications:** Patients who experienced a severe reaction to a previous dose should not receive allopurinol.[2] Discontinue at the first appearance of a rash.[2,3] (See Comments section.) Hypersensitivity reactions are rare.[3]
Infusion-related cautions	None reported.
Dosage	**Prevention/treatment of hyperuricemia secondary to neoplastic disorders:** Treatment is started 24–48 hours prior to chemotherapy.[2-5] Maintain adequate hydration to avoid potential formation of xanthine calculi and prevent renal precipitation of urates.[2,3] **<10 years of age:** 200 mg/m^2/day either as a single dose, in divided doses, or as a continuous infusion.[2-5] **10 years of age and older:** 200–400 mg/m^2/day (5–10 mg/kg/day) by continuous infusion or in equally divided intermittent IV infusions administered at 6-, 8-, or 12-hour intervals.[2-6] **Inhibition of free radical production** **Postasphyxial brain injury in newborns:** 20 mg/kg given within 4 hours of life and again 12 hours later.[7,8] Allopurinol initiated after 4 hours of life may not be beneficial in treating severe birth asphyxia.[8] **Severely hypoxic neonates on extracorporeal membrane oxygenation:** 10 mg/kg prior to cannulation followed by 5 mg/kg q 8 hr for 72 hours after initiation of bypass.[9] **Congenital heart disease necessitating cardiopulmonary bypass (CPB):** No difference in pharmacokinetic parameters or decrease in uric acid concentration has been noted in 12 neonates with hypoplastic left heart syndrome who received 5 or 10 mg/kg over 20 minutes.[10] 5 mg/kg given at least 16 hours preoperatively, 5 mg/kg given 8 hours preoperatively, 10 mg/kg given at 0700 the morning of surgery, 20 mg/kg intraoperatively via CPB circuit, and nine postoperative doses of 5 mg/kg q 8 hr decreased morbidity in neonates with hypoplastic left-heart syndrome.[11]
Dosage adjustment in organ dysfunction	**CrCl 10–20 mL/min:** 200 mg/day or reduce dosage to 50% of the usual dose.[2,3] **CrCl 3–10 mL/min:** 100 mg/day or reduce dosage to 30% of usual dose.[2,3] **CrCl <3 mL/min:** 100 mg/day at extended intervals of greater than 24 hours.[2,3]
Maximum dosage	A 3-year-old with acute lymphoblastic leukemia (ALL) received 410 mg/m^2/day for 11 days, and a 4-year-old with ALL received a cumulative dose of 8.8 g/m^2 over a 6-month period as an outpatient.[5] 600 mg/day in *adults* and children.[2]

Allopurinol Sodium

Additives	Contains ~85 mg sodium/500-mg vial.
Suitable diluents	SW to reconstitute, NS, or D5W to dilute.[2,3,11] Sodium bicarbonate–containing solutions should not be used as a diluent.[2,3,12]
Maximum concentration	≤6 mg/mL.[2,3] Two pharmacokinetics studies evaluated six healthy *adult* volunteers in each study. One study infused a single dose of 20 mg/mL over 2 minutes[13] and the other a single dose of 10 mg/mL over 15 minutes.[14]
Preparation and delivery	**Preparation:** Reconstitute by adding 25 mL SW.[2,3] The pH of the reconstituted vial ranges from 11.1 to 11.8 and must be diluted with NS or D5W.[2,3] Do not refrigerate reconstituted or diluted product. **Stability:** Administer within 10 hours of reconstitution. Contains no preservatives.
IV push	Not recommended.
Intermittent infusion	≥30 minutes.[4,5,9,10]
Continuous infusion	The daily dose may be given as a continuous infusion.[3,5]
Other routes of administration	Not indicated.
Comments	Ensure adequate urine flow by providing sufficient fluid intake.[2,3] **Adverse drug effects:** A 15-year-old boy with Williams syndrome receiving oral allopurinol for 6 weeks developed acute pure red-cell aplasia that resolved when the drug was discontinued.[15] **Drug interactions:** Azathioprine and mercaptopurine doses should be reduced by 25% to 33% and subsequent dosage based on patient response and occurrence of toxicity.[2,3] The dose may need to be increased with concomitant use of drugs that increase urate concentration.[2,3] The incidence of rash is increased with concomitant ampicillin or amoxicillin use.[2,3] Increased concentrations of cyclosporine have been reported with allopurinol use.[2,3] **Physically incompatible drugs in solution with allopurinol[2]:** Amikacin sulfate, amphotericin B, carmustine, cefotaxime sodium, chlorpromazine HCl, cimetidine HCl, clindamycin phosphate, cytarabine, dacarbazine, daunorubicin HCl, diphenhydramine HCl, doxorubicin HCl, doxycycline hyclate, droperidol, floxuridine, gentamicin sulfate, haloperidol lactate, hydroxyzine HCl, idarubicin HCl, imipenem-cilastatin sodium, mechlorethamine HCl, meperidine HCl, metoclopramide HCl, methylprednisolone sodium succinate, minocycline HCl, nalbuphine HCl, netilmicin sulfate, ondansetron HCl, prochlorperazine edisylate, promethazine HCl, sodium bicarbonate, streptozocin, tobramycin sulfate, and vinorelbine tartrate.

Alprostadil

Brand names	Prostin VR Pediatric (Prostaglandin E1, PGE1)
Medication error potential	None.
Contraindications and warnings	**U.S. boxed warning:** Apnea may occur in 10% to 12% of neonates with congenital heart defects and is seen most often in those weighing <2 kg at birth.[1] Signs and symptoms generally appear during the first hour of drug infusion.[1] The medication should only be used in places where ventilator support is available and respiratory status can be monitored. **Other warnings:** May cause gastric outlet obstruction in neonates secondary to antral hyperplasia. The effect appears to be related to the duration of therapy (i.e., >120 hr) and cumulative dose.[1–3] Infuse alprostadil at lowest effective dose and for shortest period of time while weighing the risks of long-term effects versus benefits.
Infusion-related cautions	Studies have shown that intra-aortic or intra-arterial infusion is no more effective than peripheral IV infusion. If fever or hypotension develops, the infusion rate should be slowed until resolution.[1] If apnea or bradycardia occur during the infusion, alprostadil should be discontinued and supportive therapy should be provided.[1] Cutaneous flushing is generally due to improper catheter placement and rapidly reverses with repositioning of the intra-arterial catheter.[1] Extravasation of concentrated solution may cause tissue sloughing and necrosis.[1,4]
Dosage	**Hepatic veno-occlusive disease:** 0.075 mcg/kg/hr increased q 12 hr until the maximum tolerated dose of 0.5 mcg/kg/hr has been reached.[1,5] Used in conjunction with 100 units/kg/day of heparin as a continuous infusion.[5] **Patent ductus arteriosus (PDA):** Short-term maintenance of PDA in neonates with ductal-dependent cyanotic and acyanotic congenital heart disease until surgery can be performed. 0.05–0.1 mcg/kg/min.[6–11] Although larger doses (0.4 mcg/kg/min) have been given, exceeding 0.1 mcg/kg/min generally does not provide additional benefit.[12] Early discontinuation of alprostadil following balloon atrial septostomy has been associated with an increased risk of rebound hypoxemia that necessitates reinstitution of alprostadil; hence, a graded approach to discontinuation that is based on illness severity and magnitude and duration of hypoxemia is suggested.[13] **Peripheral gangrene secondary to ischemia:** 0.05 mcg/kg/min reversed acrocyanosis of the hands and feet within 4 days.[14,15] **Pulmonary hypertension** **Heart transplant:** 0.05 mcg/kg/min during extracorporeal membrane oxygenation (ECMO). After releasing aortic cross clamps, increase to 0.1–0.15 mcg/kg/min.[16,17] **Liver transplant:** Prior to unclamping infuse 0.0125 mcg/kg/min. If hypotension occurs, double infusion to 0.025 mcg/kg/min.[18–22]
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal dysfunction.[23] One case report noted markedly larger dosage requirements (0.8 mcg/kg/min) in a newborn with ductal-dependent congential heart disease who was receiving ECMO.[24]
Maximum dosage	0.4–0.8 mcg/kg/min has been used without adverse effects, but doses of >0.1 mcg/kg/min have not improved efficacy in PDA.[1,6,24,25]

Additives

None.

Suitable diluents

Must be diluted before administration in D5W, D10W, or NS.[26]

Maximum concentration

20 mcg/mL.[26]

Preparation and delivery

Delivery system issues: Direct contact of the concentrated alprostadil solution with the wall of the plastic volumetric infusion chamber should be avoided because the drug may interact with the plastic chamber to produce a hazy solution. If this occurs, the chamber and solution should be discarded.[1,26]

Stability: Concentrated solution should be refrigerated.[26] Prepare fresh solution every 24 hours.[26]

IV push

Not recommended because of short half-life.[1]

Intermittent infusion

Not recommended because of short half-life.[1]

Continuous infusion

The manufacturer suggests the following dilutions and infusion rates to provide a dose of 0.1 mcg/kg/min.[1]

Add 1 Ampul (500 mcg) to	Approximate Concentration of Resulting Solution	Infusion Rate (mL/kg/min)	Infusion Rate (mL/kg/hr)
250	2 mcg/mL	0.05	3.0
100	5 mcg/mL	0.02	1.2
50	10 mcg/mL	0.01	0.6
25	20 mcg/mL	0.005	0.3

Other routes of administration

None.

Comments

Significant adverse effects: Because alprostadil inhibits platelet aggregation, it should be used cautiously in neonates with bleeding tendencies.[1]

Rare adverse effects: Reports of an urticarial rash[27] and "harlequin color change"[28] have been documented during alprostadil infusion in neonates with cardiac heart defects. The rash is erythematous, migratory, primarily limited to the upper torso, self-limiting, and resolve upon drug discontinuation.[25,27]

Ectopic calcifications in the deep tissues of the axillae, thoracic inlet, and neck were noted on the chest x-ray of an infant who had received a cumulative alprostadil dose of 5654 mcg/kg for documented transposition. Brown fat necrosis was confirmed on autopsy.[29]

A "pseudo-Barter syndrome" has been reported during infusions and is characterized by severe hyponatremia and polyuria, which resolves upon drug discontinuation.[1,30]

Leukocytosis has been reported and resolves with discontinuation of therapy.[31]

Cortical proliferation may develop as early as 9 days into therapy (usually 4–6 weeks) and may present as soft tissue swelling (e.g., periorbital, upper and lower extremities), peripheral hard edema, and cortical hyperostosis.[1,32–35] The changes are reversible upon alprostadil discontinuation but have taken up to 38 weeks to resolve completely.[32] It is believed that the effects are dose and duration dependent.[32–35]

Osmolality: Undiluted solution is 23,250 mOsm/kg.[26]

Amikacin Sulfate

Brand names

Amikin

Medication error potential

Look-alike, sound-alike drug names.

ISMP's *Confused Drug Names* lists confusion with Kineret.[1]

USP reports that amikacin sulfate has been confused with Amicar.[2]

Contraindications and warnings

U.S. boxed warning: Patients with impaired renal function and those receiving large doses or prolonged therapy have an increased risk for nephrotoxicity and ototoxicity (i.e., vestibular and auditory), of which ototoxicity may be irreversible.[3–5] The risk of toxicity can also be increased by prolonged elevations in serum concentrations; concurrent use of medications known to be nephro-, neuro-, or oto-toxic; dehydration; and advancing age.[3–5] Observe closely for signs or symptoms of toxicity.[3] (See Rare Adverse Effects and Monitoring in the Comments section.)

Contraindications: Known hypersensitivity to amikacin or other aminoglycosides.[3]

Other warnings: Aminoglycosides can cause neuromuscular blockade and potentiate the effects of neuromuscular blockers.[3,6,7] (See Appendix C for specific information.)

Infusion-related cautions

None.

Dosage

Although use has been questioned in pediatric patients, the following equation is recommended in *adult* obese patients receiving aminoglycosides.[8–11]

Dosing weight = IBW + 0.4 (TBW – IBW). (See Appendix B.)

Loading dose: Aminoglycoside loading doses have been advocated.[3,12–15] Limited data are available, but some advocate an initial amikacin dose of 10–17 mg/kg in neonates and infants.[3,15]

Neonates: Many studies using various dosing methods for aminoglycosides have been reported in neonates. Most reports have based recommendations on weight and postnatal age (PNA)[16–22] or gestational age.[23–39] Use of dose and interval equations based on AUC has also been recommended in the preterm neonate.[40–43] Although very few studies have been conducted using high-dose extended interval amikacin in premature neonates, traditional dosing (7.5 mg/kg/dose) has become less commonly recommended with large dose, extended interval regimens becoming accepted practice. PNA, at which any of these aminoglycoside regimens are applicable, has not been well studied, but the few studies delineating a PNA have generally been ≤7 days of age.[19,23,24,26–30,33,35,36,40]

Maintenance dose

Based on age and weight

PNA	<1200 g	1200–2000 g	≥2000 g
<7 days	7.5 mg/kg q 18–24 hr[15,22,44,45]	15 mg/kg/day divided q 12 hr[22,44,46]	15–20 mg/kg/day divided q 12 hr[3,22,46]
≥7 days	7.5 mg/kg q 18–24 hr[22]*	15–20 mg/kg/day divided q 8–12 hr[22]	30 mg/kg/day divided q 8 hr[22]

*Until 4 weeks of age.

15 mg/kg once daily has also been used in 700–1500 g, >24 weeks gestational age (WGA), preterm neonates with a PNA of ≥7 days.[15]

Dosage *(cont.)*

Based on WGA

≤28 WGA	29–36 WGA	≥37 WGA
15–20 mg/kg q 36–42 hr[47-49]	14–20 mg/kg q 24–36 hr[47-49]	15–15.5 mg/kg q 24 hr[47-50]

Infants and children: 22.5 mg/kg/day divided q 8 hr[22,44] or 1260 mg/m^2/day divided q 8 hr.[51]

Once-daily dosing outside the neonatal period: Several investigators have reported that once-daily aminoglycoside dosing has comparable efficacy and perhaps less toxicity than dosing of 8–12 hours.[52-54] A single dose of 15–25 mg/kg has been given once daily (usually over 20–30 minutes) in critically ill infants and children with severe gram-negative infections,[15,55–57] bone marrow transplantation,[58] or in febrile neutropenic patients with cancer.[59–62] Once-daily therapy has also been used to treat urinary tract infections on an outpatient basis.[63] At this time, the use of once-daily dosing in infants and children is controversial.[64] The most recent edition of the *American Academy of Pediatrics Red Book: Report of the Committee on Infectious Diseases* continues to recommend that aminoglycosides be administered in multiple daily doses in all age groups.[22]

Dosage adjustment in organ dysfunction

If CrCl is >50 mL/min, give a normal dose; if CrCl is 30–50 mL/min, give q 12–18 hr; if CrCl is 10–29 mL/min, give q 18–24 hr; and if CrCl is <10 mL/min, give q 48–72 hr.[65]

Maximum dosage

Larger doses or shorter dosing intervals of aminoglycosides are sometimes required in patients with cystic fibrosis, major thermal burns or dermal loss, or in patients with ascites.[66–69] Based on similarities between aminoglycosides, prolonged dosing interval may be required in those receiving extracorporeal membrane oxygenation.[70] Individualize dosage based on serum concentrations.

Additives

The 250-mg/mL product contains 0.319 mEq/mL of sodium bisulfate.[71] (See Appendix C for specific information about sulfite hypersensitivity.)

Suitable diluents

D5¼NS, D5½NS, D5W, LR, or NS.[3]

Maximum concentration

10 mg/mL.[72]

Preparation and delivery

Delivery system issues: The mixing of amikacin sulfate with beta-lactam antibiotic in vitro can result in substantial inactivation of the aminoglycoside. (See Appendix C for more specific information.)

Compatibility: See Appendix D for PN compatibility information.[73]

IV push

Although aminoglycosides have been given over 15 seconds,[74] 1 minute,[75] and 3–5 minutes,[76] rapid infusion is not recommended.

Intermittent infusion

Over 30–60 minutes. Infusion over 1–2 hours is recommended in infants.[3]

Continuous infusion

Not recommended. Has been given by continuous infusion.[77–79] Low serum concentrations[78] and nephrotoxicity may occur more frequently.[79]

Other routes of administration

Undiluted product for IM use.[80]

Amikacin Sulfate

Comments

Rare adverse effects: Aminoglycosides accumulate in renal cortical tissue and may damage proximal tubule cells leading to oliguric renal failure. Risk of nephrotoxicity may be influenced by type of aminoglycoside, dose, duration (cumulative dose), frequency of therapy, and elevated serum concentration.[3,4] It is also increased by advancing age, pre-existing renal or hepatic dysfunction, decrease renal perfusion, hypoalbuminemia, and dehydration.[3,4] Current administration of nephrotoxic medications may increase the risk of toxicity and should be avoided.[3]

Cochlear and/or vestibular ototoxicity has been associated with all aminoglycoside antibiotics.[5] Total AUC is a better indicator of ototoxic risk than either peak or trough serum concentration.[81,82] Use cautiously with other drugs (e.g., loop diuretics, platinum-based chemotherapeutic agents) known to cause ototoxicity.

Aminoglycosides may potentiate the curare-like effects on the neuromuscular junction and should be used with caution in patients with neuromuscular disorders since they may aggravate muscle weakness.[3,6] Aminoglycosides may enhance the respiratory depressant effect of neuromuscular-blocking agents and may prolonged blockade.[3,83,84]

Monitoring: Because large variability exists in patient response to therapy, individualize dosage based on serum concentrations, clinical response, and renal function. Recommended peak and trough serum amikacin concentration are ≤35 mg/L and ≤10 mg/L, respectively. Desired peak concentrations are dependent on the site of infection. Although serum concentration monitoring has become routine practice in many institutions, not all patients require monitoring.[85,86] Monitoring is indicated if the patient is not clinically responding, is ≤3 months of age, has disease that requires large doses or high concentrations (CNS infections, endocarditis, pneumonia, ascites, burns), has decreased or unstable renal function, or will be treated more than 10 days.

Drug interactions: Consult appropriate resources before combining any drug with gentamicin.

Laboratory interference: Serum concentrations may be falsely elevated when blood samples are collected through central venous Silastic catheters.[87]

Aminocaproic Acid

Brand names	Amicar
Medication error potential	Look-alike, sound-alike drug names. USP reports that Amicar has been confused with amikacin. No patient harm resulted. Amicar has been confused with Omacor; patient harm resulted.[1]
Contraindications and warnings	Aminocaproic acid should not be used when there is an ongoing intravascular clotting process.[2] Aminocaproic acid should not be used in hematuria of upper urinary tract origin due to the risk of thrombosis resulting in intrarenal obstruction.[2]
Infusion-related cautions	Hypotension, bradycardia, and cardiac arrhythmias may occur with rapid or undiluted administration.[2] Thrombophlebitis may occur.[2]
Dosage	**Continuous infusion:** Loading dose of 100–200 mg/kg not to exceed 5 g followed by continuous infusion at 10–33.3 mg/kg/hr or 1 g/m^2/hr.[3–14] In high-risk infants on extracorporeal membrane oxygenation (ECMO), aminocaproic acid infusion has been continued up to 72 hours during ECMO or until decannulation.[3] **Bolus dosing:** 100 mg/kg or 3 g/m^2 not to exceed 5 g q 4–6 hr or PRN.[15–19] For repair of congenital heart defects, 75 mg/kg boluses at the beginning and end of cardiopulmonary bypass along with the addition of 75 mg/100 mL of bypass priming solution has been used.[10–12] In infants undergoing congenital diaphragmatic hernia repair during ECMO, 100 mg/kg was given 30–60 minutes prior to surgery and after surgery for 24–48 hours to maintain an activated clotting time of 200–220 seconds.[15]
Dosage adjustment in organ dysfunction	Use caution in patients with cardiac, renal, or hepatic disease.[20] Reduce dose in patients with oliguria or end-stage renal disease.[20]
Maximum dosage	Total daily doses in children ≤18 g/m^2/day in children or in *adults* 30 g/day.[20] 36 g/day were given to a 12-year-old with acute lymphoblastic leukemia.[21]
Additives	Some products (multidose vials) contain benzyl alcohol. Single-use vials are preservative-free.[22] (See Appendix C for specific information about potential benzyl alcohol toxicity.)
Suitable diluents	NS, D5W, R.[2]
Maximum concentration	20 mg/mL.[2]
Preparation and delivery	Should not be administered undiluted.[2]

Aminocaproic Acid

IV push	Not recommended.[2] (See Infusion-Related Cautions section.)
Intermittent infusion	Concentration of 16–20 mg/mL is recommended by manufacturer[2] over 1 hour.[20] However, loading doses of 100 mg/kg were infused over 15–30 minutes in children 11–18 years of age.[4,5,8,13,14]
Continuous infusion	Concentration of 16–20 mg/mL is recommended by manufacturer.[2] May be infused continuously.[2–14,23]
Other routes of administration	Not indicated.
Comments	Prophylactic aminocaproic acid in children undergoing cardiac surgery reduced intraoperative blood loss but did not significantly decrease blood product transfusions.[23] Perioperative blood loss was reduced in patients during posterior spinal fusion and segmental spinal instrumentation.[4,5] Reports on the ability of aminocaproic acid to decrease the incidence of intracranial hemorrhage and other hemorrhagic complications in neonates on ECMO are conflicting.[3,6,7] **Adverse events:** A 12-year-old child with refractory thrombocytopenia after bone marrow transplantation developed myopathy after 98 days of treatment with doses ranging from 4–36 g/day.[21] Serum creatine phosphokinase concentrations, particularly in patients with myalgia, may be a useful indicator of muscle injury. Myopathy is usually reversible on discontinuation of therapy.[2,21] **Pharmacokinetic considerations:** In order to attain concentrations above the therapeutic threshold, children require larger loading and maintenance doses than *adults*.[24]

Aminophylline

Brand names	Various manufacturers
Medication error potential	Look-alike, sound-alike drug names. Aminophylline may be confused with ampicillin and amitriptyline.[1] Failure to correctly convert between aminophylline and theophylline can result in medication error.
Contraindications and warnings	**Contraindications:** Patients with a history of hypersensitivity to theophylline or other components in the product including ethylenediamine.[2] **Warnings:** Use with extreme caution as theophylline may exacerbate active peptic ulcer disease, seizure disorders, hyperthyroidism, and/or cardiac arrhythmias (not including bradyarrhythmias).[2]
Infusion-related cautions	Rapid administration may result in toxic serum concentrations[3] and circulatory failure.[4]
Dosage	Aminophylline products contain varying amounts of theophylline (check manufacturers' information). All of the doses in this monograph are reported as **THEOPHYLLINE** unless otherwise noted. **Apnea and bradycardia of prematurity (usual targeted serum concentration range of 6–12 mg/L)** **Loading dose (LD):** 4–6 mg/kg over 20–30 minutes.[3–10] If the patient is already receiving theophylline, a serum concentration must be obtained and the LD based on that concentration[11] using the equation: LD (mg/kg) = (desired concentration – measured concentration)/2 (See Other in the Comments section for more information about the equation.) **Initial maintenance dose:** 2–4 mg/kg/day divided q 12 hr[3–6] or 3.3–7.5 mg/kg/day divided q 8 hr.[7–10] **Diuretic:** Adjunctative therapy in critically ill children unresponsive to furosemide or in those who are diuretic-dependent. Low-dose *aminophylline* (loading dose of 3 mg/kg followed by 6 mg/kg/hr)[12] or theophylline (loading dose of 3 mg/kg followed by 6 mg/kg/hr).[13] **Severe acute asthma (usual "therapeutic" range 5–15 mg/L):** The role of IV aminophylline in acute asthma is controversial. Many *adult*[14–17] and pediatric[18–20] patients who respond to beta-agonist and systemic glucocorticoid experience no additional benefit from aminophylline. However, studies suggest that the addition of aminophylline may be beneficial in critically ill children with severe acute asthma and impending respiratory failure who are unresponsive to aggressive beta-agonist and systemic glucocorticoids.[21–23] *Loading*[24,25] *and maintenance*[26] *doses should be based on ideal body weight in children who are overweight or obese. (See Appendix B.)* **LD (*no* theophylline in the past 24 hours):** 5–6 mg/kg over 20–30 minutes.[2,27,28] **LD (theophylline in the past 24 hours):** A theophylline serum concentration must be obtained and the LD estimated based on the following equation (See Comments section): LD (mg/kg) = (desired concentration – measured concentration)/2[11] **Maintenance dose (initial dose to achieve a target serum concentration of 10 mg/L)** **Infants 6–52 weeks:** [0.008 (age in weeks) + 0.21] = mg/kg/hr.[28,29] **Children 1–<9 years:** 0.8 mg/kg/hr.[28]

Dosage *(cont.)*	**Children 9–<12 years:** 0.7 mg/kg/hr.[28] **Children 12–16 years (smoker):** 0.7 mg/kg/hr.[28] **Children 12–16 years (nonsmoker):** 0.5 mg/kg/hr.[28]
Dosage adjustment in organ dysfunction	Infants up to 3 months of age eliminate 50% of theophylline unchanged in the urine; hence, the dosage should be decreased in these infants.[5,28,30] The dose should also be reduced in patients with cardiac failure, hepatic dysfunction, acute hepatitis, or sustained high fever and asphyxiated neonates.[2,28,31,32]
Maximum dosage	Individualize dosage based on serum concentrations and clinical response.[2] Not to exceed 900 mg/day unless serum theophylline concentration indiciates the need for larger doses.[28]
Additives	None.
Suitable diluents	D5W, D10W, D20W, LR, NS, R, ½NS, D5NS, D5½NS, D5¼NS, D–LR, D–R, D–S, D5LR. Stable in dextran 6% in D5W, dextran 6% in NS.[33]
Maximum concentration	25 mg/mL (commercially available).[33]
Preparation and delivery	**Compatibility:** For PN compatibility information, see Appendix D.[34]
IV push	Not recommended.
Intermittent infusion	≤25 mg/mL (commercially available) over 15–30 minutes[2] not to exceed 0.36 mg/kg/min or 25 mg/min.[2,35]
Continuous infusion	≤25 mg/mL.[2] Normally diluted to 1 mg/mL.[35]
Other routes of administration	Should not be give IM.[2]
Comments	**Significant adverse effects:** *Whenever a patient receiving theophylline develops nausea or vomiting, particularly repetitive vomiting, or other signs or symptoms consistent with theophylline toxicity, the infusion should be stopped and a serum theophylline concentration measured immediately.* Death from theophylline toxicity is most often attributed to cardiorespiratory arrest and/or hypoxic encephalopathy that follows prolonged generalized seizures or intractable cardiac arrhythmias.[2,36,37] Generally, serum concentrations above 30 mg/L are associated with a variety of signs and symptoms.[36,37] Toxicities may occur at lower serum concentrations following chronic ingestion when compared to those noted after an acute ingestion.[36] Anticonvulsants should be initiated with an IV benzodiazepine (e.g., lorazepam)[2] and repetitive seizures should be treated with a long-acting anticonvulsant. Reports in animal studies suggest that phenytoin is *ineffective* in terminating theophylline-induced seizures and that phenobarbital should be used.[38,39] (See Lorazepam and Phenobarbital monographs.)

Aminophylline

Comments *(cont.)*

Monitoring: Because large variability exists in patient response to initial and maintenance doses, individualize dosage based on attainment of a "therapeutic" serum concentration and clinical response.[28] The "therapeutic range" is generally considered 5–15 mg/L for asthma and 6–12 mg/L for apnea.[40] Concentrations up to 20 mg/L have been used in acute asthma.[41]

Drug interactions: Theophylline is a substrate of CYP1A2 (major), 2E1 (minor), and 3A4 (minor) and may be associated with many potentially fatal drug interactions.[35] Consult appropriate resources for dosing recommendations before combining any drug with theophylline.

Laboratory interference: When measured by the Bittner or colorimetric method, theophylline produces false–positive elevations of serum uric acid.[2] No inference is noted when other methods are employed. May also decrease serum concentrations of triiodothyronine.[2]

Other: The equation to calculate LD assumes a normal volume of distribution of 0.5 L/kg). As a general rule, 1 mg/kg of theophylline will increase the serum theophylline concentration by 2 mg/L.[11]

Amphotericin B

Brand names	Fungizone, Amphocin, generic
Medication error potential	Look-alike, sound-alike drug names. ISMP reports that amphotericin B has been confused with Abelcet and AmBisome.[1] USP reports that amphotericin B has been confused with amphotericin B liposome; patient harm resulted. USP also reports that Fungizone has been confused with AmBisome; no patient harm resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** Reserve treatment with amphotericin B for progressive and potentially life-threatening fungal infections; do not use for noninvasive fungal infections in immunocompetent patients.[3] Do not give a dose >1.5 mg/kg. Overdose may result in potentially fatal cardiac arrest or cardiopulmonary syndrome.[3] Verify the product name, dosage and preadministration, especially if the dose >1.5 mg/kg.[3] **Contraindications:** Amphotericin B therapy is complicated by many dangerous side effects. It is contraindicated in patients with hypersensitivity to amphotericin B or any of its components, unless benefit of treating life-threatening disease outweighs potential risk.[3]
Infusion-related cautions	Hypersensitivity reactions, including anaphylaxis, have been reported.[4–6] Other infusion-related symptoms include fever, chills, nausea, vomiting, headache, malaise, hypotension and arrhythmias.[7] Patients have been premedicated with acetaminophen, codeine, diazepam, diphenhydramine, hydroxyzine, meperidine, or prochlorperazine.[8–10] Corticosteroids have been added to amphotericin B solutions to decrease the incidence and severity of febrile response during infusion.[8,11] However, congestive heart failure has been reported in *adults* who received 25–40 mg/day of hydrocortisone with amphotericin B.[8] Although amphotericin B is incompatible with fat emulsion (FE),[12] it has been reconstituted in a small volume of D5W and then diluted in 20% intravenous FE (IVFE) in order to improve tolerance and decrease infusion-related side effects in *adults*.[13,14] Thrombophlebitis and injection pain may also occur; adding 1 unit of heparin per mL of solution may reduce pain at the injection site and phlebitis.[15] Arrhythmias have been reported during infusion in a neonate.[16] Although cardiovascular collapse has occurred in animals after rapid injection,[17,18] it has been infused over 45–60 minutes without problems in *adults.*[19–21]
Dosage	**Initial and maintenance:** 0.25–0.5 mg/kg q 24 hr infused over 2–6 hours. Increase daily dose as tolerated by 0.25–0.5 mg/kg up to 0.5–1.5 mg/kg q 24 hr.[7,11,22–37] Early studies, many administering amphotericin B in combination with flucytosine, used smaller initial doses and slower dose titration.[38–45] Recent data supports the use of larger doses initially (0.25–0.5 mg/kg q 24 hr) followed by a more rapid dose titration to achieve the desired therapeutic dose.[7,23,26,28] **Test dose (to minimize anaphylactic response in susceptible individuals):** Although one study in *adults*, who were frequently premedicated, failed to show that a test dose predicted anaphylactic reactions,[4] a single dose of 0.1 mg/kg, up to 1 mg, infused over 20–60 minutes is often used.[3,38,41,44,46] Vital signs should be monitored every 30 minutes for 2 hours. If a test dose is done, therapy should commence the same day with the remainder of a recommended therapeutic dose.[17]

Dosage *(cont.)*	Pharmacokinetic data suggest great variability in clearance, volume of distribution, and half-life in neonates, particularly premature neonates.[28,46,47] Some papers have advocated smaller and/or less frequent doses in neonates.[46,48,49] Doses of 0.5 mg/kg and dosing intervals >24 hours may be appropriate for these patients.[42,45,46] One study used an every-other-day dosing regimen with 0.5 mg/kg in neonates <1 kg or 1 mg/kg in neonates ≥1 kg.[50]
Dosage adjustment in organ dysfunction	Dose adjustment is not necessary in patients with renal insufficiency[7,51]; however, if renal insufficiency occurs during therapy, the dosing interval should be increased or alternate day dosing should be done prior to a decrease in the total daily dose.[7,51] Alternately, therapy may be changed to an amphotericin B lipid product.
Maximum dosage	Total daily dose should not exceed 1.5 mg/kg.[3,7] Doses of 1.5 mg/kg/day for an unspecified time[46] and 1.3 mg/kg/day for 31 days[36] have been used in children. Reported cumulative doses in pediatric patients have ranged from 2.5 to 52 mg/kg.[24,28–30,32–34,39,41–43,52] Larger doses (>1 mg/kg) may be associated with increased risk of nephrotoxicity, which can present as oliguria, azotemia, increased SCr, potassium wasting, and renal tubular acidosis. GFR was reduced permanently in *adults* who received >4 g over the course of therapy.[8,17,53] Pediatric patients have received total cumulative doses of 30–52 mg/kg without evidence of "permanent" nephrotoxicity.[30,32,33] Evidence does not support serum drug concentration or cumulative dose monitoring as a marker of toxicity.[54] (See Comments section.) Three children who inadvertently received doses of 3.8, 4.6, or 5 mg/kg and two premature neonates who received 25 and 40.8 mg/kg experienced cardiac arrest during or shortly after the infusion. Only one child survived.[55]
Additives	None reported.
Suitable diluents	D5W, D10W, D15W, or D20W.[12]
Maximum concentration	0.1 mg/mL.[3,12] The osmolality of this solution (0.1 mg/mL in D5W) is 256 mOsm/kg.[12] While one reference states that a concentration of 0.25 mg/mL may be given in fluid-restricted patients via a central catheter,[56] more concentrated solutions increase the risk of phlebitis.[57] Concentrations as high as 0.5–1 mg/mL have been found to be chemically stable for up to 120 hours when stored at 4°C.[58]
Preparation and delivery	**Filtration:** If in-line filtration is indicated, use filters with a pore size ≥1 micron.[12]
IV push	Not reported.
Intermittent infusion	0.1 mg/mL in D5W, D10W, D15W, or D20W[12,59] over 2–6 hours.[12,17] Shorter infusion times (1–2 hours) have been tolerated in older children and *adults* and may improve drug delivery.[7]
Continuous infusion	Not reported.
Other routes of administration	Amphotericin B has also been given via IT route as well as intra-articularly, intrapleurally, intraventricular,[60] aerosolized,[61] and by irrigation.[12]

Amphotericin B

Comments

Significant adverse effects: Concomitant nephrotoxic drugs may increase the potential for nephrotoxicity.[49,51] Hydration and sodium repletion, either through sodium loading with NS over 30 minutes prior to administration or with sodium intakes of >4 mEq/kg/day, may reduce the risk of nephrotoxicity.[7,51,62] Because rifampin acts synergistically with amphotericin B, they have been given concomitantly to reduce the amphotericin B dose and, hence, the risk of nephrotoxicity.[63]

Hypokalemia and renal tubular acidosis may occur.[7]

Pharmacokinetic considerations: See Dosage section.

Amphotericin B Cholesteryl Sulfate Complex

Brand names	Amphotec
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error (liposomal forms of drugs).[1] The product name and dosage should be verified prior to dispensing and administration.
Contraindications and warnings	Should not be used in patients with a hypersensitivity to any of the drug components.[2]
Infusion-related cautions	Anaphylaxis has been reported.[2] Acute reactions (hypotension, fever, chills) may occur within 1–3 hours after administration. Infusion-related reactions may be managed by decreasing the rate of infusion or by premedicating with antihistamines or corticosteroids.[2] Stop infusion immediately in cases of severe respiratory distress.[2]
Dosage	Amphotericin B cholesteryl sulfate complex has also been referred to as amphotericin B colloidal dispersion (ABCD) in clinical studies and case reports. **Systemic fungal infections (*Aspergillus* sp., *Candida* sp., and *Cryptococcus* sp.) in patients refractory or intolerant to conventional amphotericin B because of adverse effects, including nephrotoxicity** **Children and adolescents:** 3–6 mg/kg/day.[3–8] One study in premature neonates gave 3 mg/kg/day on day 1 followed by 5 mg/kg/day thereafter.[9] The manufacturer recommends administration of a test dose (10 mL of the final preparation containing between 1.6 and 8.3 mg) to be given over 15–30 minutes while observing the patient for tolerance.[2]
Dosage adjustment in organ dysfunction	No dosage adjustment recommended for hepatic or renal impairment (CrCl ≥35 mL/min). No information on dosage adjustment in more severe hepatic or renal disease.[2]
Maximum dosage	6 mg/kg/day.[3] However, doses as high as 7.5 mg/kg/day have been used.[2]
Additives	None reported.
Suitable diluents	Reconstitute with SW (5 mg/mL); dilute further with D5W.[2,10]
Maximum concentration	0.83 mg/mL.[2,10]
Preparation and delivery	Do not mix lipid-based amphotericin B products with other IV medications or saline or coadminister with other parenteral solutions containing saline or electrolytes.[2,10] Do not filter or use an in-line filter during administration.[2,10]
IV push	Not recommended.[2]

Amphotericin B Cholesteryl Sulfate Complex

Intermittent infusion	Dilute reconstituted drug with D5W to a final concentration of 0.6 mg/mL (range 0.16–0.83 mg/mL).[2,10] Infuse at a rate of 1 mg/kg/hr.[2,10] May infuse over a minimum of 2 hours in patients exhibiting no adverse effects.[2,10]
Continuous infusion	Not reported.
Other routes of administration	Not reported.
Comments	Hepatotoxicity has been reported.[2] There is some evidence that the colloidal dispersion formulation may be the least tolerable of the available amphotericin B lipid formulations.[11]

Amphotericin B Lipid Complex

Brand names	Abelcet
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error (liposomal forms of drugs).[1] The product name and dosage should be verified prior to dispensing and administration. Look-alike, sound-alike drug names. USP reports that amphotericin B lipid complex has been confused with amphotericin B desoxycholate; no patient harm resulted.[2] ISMP reports that Abelcet has been confused with amphotericin B.[3] USP reports that Abelcet has been confused with Ambisome; patient harm and death resulted.[2]
Contraindications and warnings	Should not be used in patients with a hypersensitivity to any of the drug components.[4]
Infusion-related cautions	Anaphylaxis has been reported.[4] Acute reactions (hypotension, fever, chills) may occur within 1–2 hours after administration.[4] Infusion-related reactions may be managed by decreasing the rate of infusion or by premedicating with antihistamines or corticosteroids. Stop infusion immediately in cases of severe respiratory distress.[4] Chest discomfort has been reported.[5] Hypertension has been reported in an *adult*.[6]
Dosage	**Empiric treatment of febrile neutropenic patients:** 5 mg/kg/day has been studied in children 2–16 years of age.[5] **Systemic fungal infections (*Aspergillus* sp., *Candida* sp., and *Cryptococcus* sp.) in patients refractory or intolerant to conventional amphotericin B because of adverse effects, including nephrotoxicity** **Neonates, infants, and children 2–17 years:** 2.5–5 mg/kg/day.[4,7–11] One study in neonates gave up to 6.5 mg/kg/day.[12]
Dosage adjustment in organ dysfunction	The need for dosage adjustment with amphotericin B lipid complex in hepatic or renal impairment is not known.[4] Dosage adjustments have not been recommended for renal insufficiency.[13]
Maximum dosage	5 mg/kg/day.[4,7] However, doses as high as 6.5–13 mg/kg have been given to children and *adults*.[4,10,12,14,15]
Additives	Each mL contains 9 mg NaCl.[4,16]
Suitable diluents	D5W.[4,16]
Maximum concentration	2 mg/mL.[4,16]

Amphotericin B Lipid Complex

Preparation and delivery	Add desired dose of amphotericin B lipid complex, using the 5-micron filter needle supplied with each vial, to D5W to make a final concentration of 1–2 mg/mL (usual concentration is 1 mg/mL).[4,16] Do not mix lipid-based amphotericin B products with other IV medications, saline, or coadminister with other parenteral solutions containing saline or electrolytes.[4,16] Do not use an in-line filter during administration.[4,16] Shake bag thoroughly before infusion.[4,16]
IV push	Not recommended.[4,16]
Intermittent infusion	Infuse at a rate of 2.5 mg/kg/hr. If >2 hours is required to administer a given dose, shake the bag to mix contents q 2 hr.[4]
Continuous infusion	Not reported.
Other routes of administration	Not reported.
Comments	Hepatotoxicity has been reported.[7] Nephrogenic diabetes insipidus has been reported in an *adult* patient receiving 5/mg/kg/day of amphotericin B lipid complex.[18]

Amphotericin B Liposomal

Brand names	AmBisome
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error (liposomal forms of drugs).[1] The product name and dosage should be verified prior to dispensing and administration. Look-alike, sound-alike drug names. USP reports that amphotericin B liposomal has been confused with amphotericin B; patient harm resulted.[2] ISMP reports that AmBisome has been confused with amphotericin B.[3] USP reports that AmBisome has been confused with Fungizone; no patient harm resulted.[2] USP also reports that AmBisome has been confused with Abelcet; patient harm resulted.[2]
Contraindications and warnings	Should not be used in patients with a hypersensitivity to any of the drug components.[4]
Infusion-related cautions	Acute infusion-related reactions (chest pain; dyspnea; hypoxia; severe abdomen, flank, or leg pain; and flushing and urticaria) may occur within the first 5 minutes of infusion and are not related to infusion rate. Use diphenhydramine and infusion interruption to manage these acute reactions. Acute reactions (hypotension, fever and chills) that occur with conventional amphotericin B may still occur within 1–2 hours after the administration of liposomal amphotericin B, but with decreased frequency.[4–6] Anaphylaxis has been reported. Stop infusion immediately in cases of severe anaphylactic reaction.[4]
Dosage	**Empiric treatment of febrile neutropenic patients** **Children and adolescents:** 3 mg/kg/day.[7,8] **Solid organ and bone marrow transplant prophylaxis/treatment** **Children and adolescents:** 2–6 mg/kg/day over a mean of 25 days (range 5–90 days).[9–12] 10 mg/kg once weekly may provide useful prophylaxis against fungal infections as described in 14 children (4.5 months to 9 years of age) undergoing hematopoietic stem cell transplant.[13] **Systemic fungal infections (*Aspergillus* sp., *Candida* sp., and *Cryptococcus* sp.) in patients refractory or intolerant to conventional amphotericin B because of adverse effects, including nephrotoxicity** **Neonates (term and preterm), infants, children, and adolescents:** 3–5 mg/kg/day.[14–25] Doses in neonates have been reported as high as 7 mg/kg/day.[20–22] Up to 10 mg/kg/day in pediatric patients and 15 mg/kg/day in *adults* has been found to be well tolerated and effective for treatment of aspergillosis and other filamentous fungal infections.[4,26] **Visceral leishmaniasis** **Immunocompetent children and adolescents**[4,27–29]**:** 3 mg/kg/day on days 1–5 and on days 14 and 21 of therapy. Alternatively, 4 mg/kg has been given on days 1–5 and on day 10 of therapy. Mediterranean visceral leishmaniasis has been successfully treated with 20 mg/kg given either as 4 mg/kg for 5 days or 10 mg/kg for 2 days.[29] **Immunocompromised children and adolescents**[4]**:** 4 mg/kg/day on days 1–5 and on days 10, 17, 24, 31, and 38 of therapy.

Amphotericin B Liposomal

Dosage adjustment in organ dysfunction	The need for dosage adjustment in hepatic impairment is not known. It has been given successfully to patients with pre-existing renal impairment.[4]
Maximum dosage	10 mg/kg/day in children; 15 mg/kg/day in *adults.*[4,26]
Additives	Each vial contains 0.64 mg alpha tocopherol.[4,30]
Suitable diluents	The manufacturer recommends dilution in D5W.[4] Another reference reports stability in D5W, D10W, D20W, and D25W.[30]
Maximum concentration	2 mg/mL.[4,30]
Preparation and delivery	**Preparation:** After reconstituting with SW and shaking vigorously, add desired dose of liposomal amphotericin B, using the 5-micron filter needle provided with each vial, to suitable diluent to make a final concentration of 1–2 mg/mL (more dilute concentrations of 0.2–0.5 mg/mL may also be used).[4,30] **Stability:** Administration should begin within 6 hours of dilution per the manufacturer.[4] **Delivery:** Do not mix lipid-based amphotericin B products with other IV medications or saline or coadminister with other parenteral solutions containing saline or electrolytes.[18] An in-line filter that is ≥1 micron may be used.[4,20]
IV push	Not recommended.[4]
Intermittent infusion	Infuse over 2 hours. May infuse over 1 hour in patients exhibiting no adverse effects.[4,30]
Continuous infusion	Not reported.
Other routes of administration	Not reported.
Comments	Hepatotoxicity has been reported.[14] Hyperphosphatemia has been reported with liposomal amphotericin in patients receiving standard doses (5 mg/kg/day, n = 2) as well as high-dose therapy (10–25 mg/kg/day, n = 3). Underlying renal insufficiency may play a role. The phospholipid carrier is the presumed source of the phosphate. Liposomal amphotericin B provides 37 mg inorganic phosphate per 50 mg amphotericin, whereas amphotericin B lipid complex provides 6.8 mg per 50 mg drug.[31,32] Nephrogenic diabetes insipidus has been reported in three patients receiving high-dose (10 mg/kg/day) liposomal amphotericin B. Symptoms resolved after discontinuation of the drug.[33] Systemic liposomal amphotericin B in combination with liposomal amphotericin B central venous catheter lock therapy (3-mL solution of 8 mg drug in D5W with 200 units heparin) has successfully treated fungal central venous catheter infections in pediatric patients (6 months to 7 years of age).[34]

Ampicillin Sodium

Brand names

Multiple generics available

Medication error potential

Look-alike, sound-alike drug names.

USP reports that ampicillin sodium has been confused with aminophylline, Augmentin, cefazolin, nafcillin, oxacillin, penicillin G sodium, piperacillin, and Unasyn.[1]

Contraindications and warnings

Contraindications: Hypersensitivity to ampicillin or other penicillins or any component of the formulation.[2]

Warnings: Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[2] These are more likely in patients who are sensitive to multiple allergens (e.g., asthma) and in those with a history of type I reaction to penicillin or cephalosporins.[2] (See Appendix C for specific information.)

Infusion-related cautions

If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.[2]

Dosage

Neonates

PNA	≤1200 g	1200–2000 g	≥2000 g
<7 days	50–100 mg/kg/day divided q 12 hr[3]*	50–100 mg/kg/day divided q 12 hr[3]	75–150 mg/kg/day divided q 8 hr[3]
≥7 days		75–150 mg/kg/day divided q 8 hr[3]	100–200 mg/kg/day divided q 6 hr[3]

*Until 4 weeks of age.

Infants and children

Mild-to-moderate infections: 100–150 mg/kg/day divided q 6 hr up to 4 g/day.[3]

Severe infections: 200–400 mg/kg/day divided q 6 hr up to 12 g/day.[3]

Bacterial endocarditis (prophylaxis)

Dental, oral, respiratory tract, or esophageal procedures*: 50 mg/kg (up to 2 g) given as a single dose, 30–60 minutes before a procedure.[4,5] Only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome. (See Comments section.)

**Procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.*[4,5]

Bacterial endocarditis (treatment)

Enterococcal endocarditis (sensitive to penicillin, gentamicin and vancomycin): 300 mg/kg/day divided q 4–6 hr plus gentamicin 3 mg/kg/day divided q 8 hr.[5] If symptom ≤3 months treat for 4 weeks and if >3 months treat for 6 weeks.[5]

Meningitis

≤7days and >1200 g: 100–300 mg/kg/day divided q 8–12 hr.[6,7]

>7–28 days and ≥1200 g: 150–300 mg/kg/day divided q 6–8 hr.[6,7]

Infants and children: 200–400 mg/kg/day divided q 6 hr up to 6–12 g/day.[3,7-9]

Ampicillin Sodium

Dosage adjustment in organ dysfunction	If CrCl is 10–29 mL/min, give normal dose q 8–12 hr, and if CrCl <10 mL/min, give normal dose q 12 hr.[10]
Maximum dosage	400 mg/kg/day.[11]
Additives	2.9–3.1 mEq sodium/g of ampicillin.[12]
Suitable diluents	LR, NS, D5W, D5½NS, or SW.[2,12]
Maximum concentration	100 mg/mL in NS or 125 mg/mL in SW for direct IV administration,[2] 30 mg/mL[2,12] in SW for peripheral line administration, and up to 112 mg/mL in fluid-restricted patients.[12]
Preparation and delivery	**Delivery system issues:** The mixing of ampicillin with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[2,12] (See Appendix C for more specific information.) **Stability:** IM or direct IV products should be used within 1 hour; if dextrose is used as a diluent the resulting solution is only stable for 2 hours versus 8 hours if prepared with NS.[2, 12] **Compatibility:** For PN compatibility information, please see Appendix D.[13]
IV push	Up to 500 mg may be given over 3–5 minutes, and up to 2 g may be administered over 10–15 minutes. More rapid administration is not recommended due to seizures.[2]
Intermittent infusion	≤30 mg/mL and dose >500 mg over 10–15 minutes.[12]
Continuous infusion	Not recommended.
Other routes of administration	≤250 mg/mL in SW or BW has been given IM but must be used within 1 hour.[12]
Comments	**Rare adverse events:** In a study of 14 very low birth weight neonates (<750 g and <28 weeks gestational age), the authors conclude that 50 mg/kg q 18–24 hr sufficiently kill bacteria while reducing the risk of ampicillin-associated seizures.[14] Neurotoxic (e.g., lethargy, confusion, twitching, multifocal myoclonus, and localized or generalized epileptiform seizures) may occur with large doses, especially in patients with renal insufficiency.[15,16] Ampicillin has been reported to prolong bleeding time in very low birth weight infants.[17] A high percentage (43% to 100%) of patients with infectious mononucleosis develop a maculopapular, trunk skin rash that spreads while receiving ampicillin.[2] The rash generally appears 7–10 days after the start of ampicillin and persist for a few days to a week following drug discontinuation.[2] It is not known whether these patients are truly allergic to ampicillin, but the drug is not recommended in patients with mononucleosis. **Drug interactions:** Coadministration with allopurinol may increase the incidence of rash with both drugs.[2] Consult appropriate resources for dosing recommendations before combining any drug with ampicillin.

Ampicillin Sodium

Comments *(cont.)*

Laboratory interference: Ampicillin may cause false–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used.[2]

Other: Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable: (1) prosthetic cardiac valve or prosthetic material used for cardiac valve repair; (2) previous infective endocarditis; (3) congenital heart disease (CHD) in a person with a) unrepaired cyanotic CHD, including palliative shunts and conduits, b) completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure, or c) repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization); and (4) cardiac transplantation recipients who develop cardiac valvulopathy.[4]

Ampicillin Sodium–Sulbactam Sodium

Brand names	Unasyn
Medication error potential	Look-alike, sound-alike drug names. USP reports that ampicillin sodium–sulbactam sodium has been confused with aminophylline, ampicillin, Augmentin, cefazolin, nafcillin, oxacillin, penicillin G sodium, and piperacillin.[1] Unasyn has been confused with ampicillin, Levaquin, and Zosyn. Confusion with ampicillin has resulted in patient harm.[1]
Contraindications and warnings	**Contraindications:** Hypersensitivity to any of the penicillins.[2] **Warnings:** Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[2] These are more likely in patients who are sensitive to multiple allergens and in those with a history of type I reaction to penicillin or cephalosporins.[2] (See Appendix C for specific information.) Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management. Thrombophlebitis and pain at the injection site may occur.[2]
Dosage	Dosage based on *ampicillin* component.[2] 1.5 g contains 1 g of ampicillin and 0.5 g of sulbactam. Sulbactam is a beta-lactamase inhibitor that extends the spectrum of ampicillin but has little antibacterial activity.[2] The American Academy of Pediatrics and the manufacturer state that safety and efficacy has only been established in those >1 year of age.[2,3] Pediatric patients who weigh ≥40 kg may receive the usual *adult* dose.[2] **Mild-to-moderate infections:** 100–150 mg/kg/day of ampicillin divided q 6 hr.[3–6] **Severe infections:** 200–400 mg/kg/day of ampicillin divided q 6 hr.[3,7–11] **Bacterial endocarditis (treatment)** **Culture negative and native valve:** 300 mg/kg/day of ampicillin divided q 4–6 hr plus gentamicin (3 mg/kg/day divided q 8 hr) for 4–6 weeks.[12] **Enterococcal endocarditis (resistant to penicillin and susceptible to aminoglycoside and vancomycin):** 300 mg/kg/day of ampicillin divided q 6 hr plus gentamicin (3 mg/kg/day divided q 8 hr) for 6 weeks.[12] **HACEK microorganisms:** 300 mg/kg/day of ampicillin divided q 4–6 hr.[12] Treat for 4 weeks unless prosthetic material is present then treat for 6 weeks.[12]
Dosage adjustment in organ dysfunction	If CrCl is 30–50 mL/min, give 35–50 mg/kg q 8 hr; if CrCl is 10–29 mL/min, give 35–50 mg/kg q 12 hr, and if CrCl <10 mL/min, give 35–50 mg/kg q 24 hr.[13]
Maximum dosage	400 mg/kg/day[3] up to 8 g/day of ampicillin.[2] Total daily sulbactam dose should not exceed 4 g.[2]

Ampicillin Sodium–Sulbactam Sodium

Additives	1.5 g ampicillin contains 115 mg (5 mEq) of sodium.[14]
Suitable diluents	D5½NS, D5W, NS, SW, LR.[14]
Maximum concentration	30 mg/mL for IV and 250 mg/mL for IM administration.[2,14]
Preparation and delivery	**Delivery system issues:** The mixing of ampicillin with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[2] (See Appendix C for more specific information.) **Stability:** 20 mg/mL of ampicillin in D5W is stable at room temperature for 2 hours and 30 mg/mL in NS, SW, and LR is stable at room temperature for 8 hours.[2,14] 2 mg/mL in D5½NS is stable at room temperature for 4 hours.[2,14] IM administration preparation should be used within 1 hour.[2,14] **Compatibility:** See Appendix D for PN compatibility information.[15]
IV push	Ampicillin sodium sulbactam should be administered over 10–15 minutes.[2,14]
Intermittent infusion	Larger dilutions of 50–100 mL given over 15–30 minutes.[2,14]
Continuous infusion	Not administered by this method.
Other routes of administration	250 mg/mL of ampicillin can be administered IM in SW or lidocaine 0.5% to 2%.[14] The safety and efficacy via IM administration in pediatric patients have not been established.[2]
Comments	**Rare adverse events:** Neurotoxicities may occur with large doses, especially in patients with renal insufficiency.[16] Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. A high percentage (43% to 100%) of patients with infectious mononucleosis develop a maculopapular, trunk skin rash that spreads while receiving ampicillin.[2,17] The rash generally appears 7–10 days after the start of ampicillin and persists for a few days to a week after discontinuation.[2] It is not known whether these patients are truly allergic to ampicillin, but the drug is not recommended in patients with mononucleosis. **Drug interactions:** Probenecid may decrease the tubular secretion of ampicillin and sulbactam and increase its concentration in the serum.[2] Consult appropriate resources for dosing recommendations before combining any drug with ampicillin–sulbactam. **Laboratory interference:** Ampicillin may cause false–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used.[2] Some individuals have developed a positive direct Coombs test during treatment.[2]

Anidulafungin

Brand names	Eraxis
Medication error potential	None reported by ISMP or USP.[1–3]
Contraindications and warnings	**Contraindications:** Patients with known hypersensitivity to the drug or any of its components, or to other echinocandins.[4] **Warnings:** Clinically significant hepatic abnormalities (hepatic dysfunction, hepatitis and hepatic failure) may occur.[4]
Infusion-related cautions	Histamine-mediated symptoms (rash, urticaria, flushing, pruritus, dyspnea, and hypotension) have been reported. These symptoms occur infrequently if infusion rate is ≤1 mg/min.[4] A 16-year-old developed moderate facial erythema and rash at the start of anidulafungin infusion that resolved within 1.5 hours of stopping the infusion. These symptoms did not recur with repeat infusion and continuation of therapy.[5]
Dosage	Experience with anidulafungin in children, particularly neonates, is limited[6]; currently there is no established dose range for pediatric patients.[7] One study demonstrated that neonates and infants receiving anidulafungin 1.5 mg/kg/day achieve serum concentrations similar to those achieved in *adults* receiving 100 mg/day.[8] **Neonates and infants <2 years (treatment/prophylaxis)** **Loading dose[10]:** 3 mg/kg. **Maintenance dose[10]:** 1.5 mg/kg given once daily. **Children 2–17 years (treatment/prophylaxis)** **Loading dose[5,6]:** 1.5 mg/kg (not to exceed 100 mg) or 3 mg/kg (not to exceed 200 mg). **Maintenance dose[5,6]:** 0.75 mg/kg (not to exceed 50 mg) or 1.5 mg/kg (not to exceed 100 mg) given once daily. The above dosage regimens were found to produce similar concentrations as that seen in *adults* receiving maintenance therapy with 50 or 100 mg/day.[5]
Dosage adjustment in organ dysfunction	No dosage adjustment in renal or hepatic dysfunction.[4,9]
Maximum dosage	**Loading dose[4,5]:** 200 mg/day in children and *adults*. **Maintenance dose[4,5]:** 100 mg/day in children and *adults*.
Additives	None.
Suitable diluents	D5W or NS.[4,10]
Maximum concentration	0.77 mg/mL.[4,10]

Anidulafungin

Preparation and delivery	The anidulafungin powder is insoluble in water and slightly soluble in ethanol. Reconstitute with companion diluent (15 mL or 30 mL 20% w/w dehydrated alcohol in water for injection), then further dilute with D5W or NS to a concentration of 0.77 mg/mL.[4,9] **50 mg/65-mL dose:** 15 mL of reconstituted drug and 50 mL diluent.[4] **100 mg/130-mL dose:** 30 mL of reconstituted drug and 100 mL diluent.[4] **200 mg/260-mL dose:** 60 mL of reconstituted drug and 200 mL diluent.[4] Use the solution immediately. If refrigerated at 2°C to 8°C, solution may be used up to 24 hours after preparation.[4]
IV push	Not recommended.
Intermittent infusion	Infuse over 45 minutes to 3 hours at a rate not to exceed 1.1 mg/min.[4,5,10]
Continuous infusion	Not reported.
Other routes of administration	Not reported.
Comments	Anidulafungin has been given empirically to neutropenic children (2–17 years) for 1–23 days (mean 8.7 days); none of the children developed a fungal infection.[5] The most common adverse drug effects were fever, feeling abnormal, rash/erythema, increased BUN, and hypotension. Most adverse effects in children receiving larger doses occurred in children $<$11 years of age.[5]

Antihemophilic Factor (Human)

(Factor VIII)

Brand names

Hemophil M, Koāte-DVI, Monoclate-P

Medication error potential

Factor VIII may be confused with Factor XIII.[1]

Contraindications and warnings

Contraindications: Hypersensitivity or intolerance to any component in the product.[1–4] Product-specific contraindications: Hemofil M, Monoclate P, hypersensitivity to mouse protein.[2,4]

Other warnings: Hemofil M contains latex in product packaging: avoid use in patients with latex allergy.[2] Koāte-DVI contains polysorbate 80, which may cause allergic reactions in susceptible individuals, especially neonates.[3]

Human antihemophilic factor (AHF) products are prepared from human pooled plasma and may carry a risk for transmission of infectious agents, despite viral attenuation processes.[2–6] Hepatitis A and B vaccination are recommended in all hemophilia patients.[5]

Progressive anemia and hemolysis may occur when large or frequent doses of human AHF are administered to patients with blood groups A, B, and AB, due to trace amounts of blood group A and B isohemagglutinins.[1,4]

Patients treated with AHF products should be carefully monitored for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of these products, predominantly children <5 years of age. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures Factor VIII inhibitor concentration should be performed.[1–5]

Infusion-related cautions

All products have been associated with anaphylaxis-type reactions. Reduce infusion rate or temporarily discontinue if patient experiences tachycardia or allergic-type reaction.[1–4]

Dosage

Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment: For every 1 International Unit/kg body weight of product administered, Factor VIII level should increase by 2%; calculated dose should be adjusted to the actual vial size.[1–4]

Formula to calculate dosage required, based on desired increase in Factor VIII (% of normal). **Note:** This formula assumes that the patient's baseline AHF level is <1%): International Units required = body weight (kg) × 0.5 × desired increase in Factor VIII (International Units/dL or % of normal).[1–4]

Consult individual product labeling for specific dosing recommendations.[2–4]

Minor hemorrhage (required peak postinfusion AHF level, 20% to 40%): 10–20 International Units/kg; repeat q 12–24 hr for 1–3 days until bleeding is resolved or healing is achieved. Mild superficial or early hemorrhage may respond to a single dose.[2–4]

Moderate hemorrhage (required peak postinfusion AHF level, 30% to 60%): 15–30 International Units/kg; repeat q 12–24 hr for 3–4 days until pain and disability are resolved.[2–4]

Severe/life-threatening hemorrhage

Hemofil M (required peak postinfusion AHF level, 60% to 100%): 30–50 International Units/kg; repeat q 8–24 hr until threat is resolved.[1,2]

Antihemophilic Factor (Human)

Dosage *(cont.)*

Koāte-DVI, Monoclate P (required peak postinfusion AHF level, 80% to 100%)

Initial: 40–50 International Units/kg.

Maintenance: 20–25 International Units/kg q 8–12 hr until bleeding is resolved.[3,4]

Minor surgery (required peak postinfusion AHF level, 30% to 80%): 15–40 International Units/kg; dose depends on procedure and specific product recommendations. For some procedures, a single dose plus oral antifibrinolytic therapy within 1 hour is sufficient; other procedures may require repeated doses q 12–24 hr until bleeding is resolved.[1–3]

Monoclate P (required peak postinfusion AHF level, 30% to 50%)

Initial dose: 15–25 International Units/kg.

Maintenance dose: 10–15 International Units/kg q 8–12 hr.[4]

Major surgery (required peak pre- and postoperative AHF level, 80% to 100%): 40–50 International Units/kg 1 hour prior to surgery; repeat 18–24 hr depending on healing.[1]

Hemofil M (required peak pre- and postsurgery AHF level, 80% to 100%): Give sufficient dose 1 hour prior to surgery; repeat q 8–24 hr depending on state of healing.[2]

Koāte-DVI (required peak pre- and postsurgery AHF level, 100%): 50 International Units/kg; repeat q 6–12 hr initially and until healing complete (10–14 days).[3]

Monoclate P (required peak pre- and postsurgery AHF level, 80% to 100%): Give sufficient dose 1 hour prior to surgery. Second dose, 50% of first priming dose should be administered 5 hours after first dose. Factor levels should be maintained to minimum of at least 30% for 10–14 days postoperatively to maintain hemostasis.[4]

Prophylaxis: May be given on a regular schedule to prevent bleeding, usually administered 3 times a week. Dose should be individualized based on age, venous access, activity, and availability of clotting factor concentrates. Prophylactic therapy is reserved for patients with severe hemophilia. Goal is to maintain Factor VIII levels >1 International Unit/dL.[5,7,8]

Dosage adjustment in organ dysfunction

No dosage adjustment required.[2–4]

Maximum dosage

None reported.

Additives

Hemofil M: Albumin, polyethylene glycol, histidine, glycine, mouse protein, tri-n-butyl phosphate, octoxynol 9.[2]

Koāte-DVI: Albumin, polyethylene glycol, glycine, polysorbate 80, tri-n-butyl phosphate, calcium, aluminum, histidine.[3]

Monoclate-P: Albumin, sodium (300–450 mM/L), calcium chloride, mannitol, histidine, mouse protein.[4]

Suitable diluents

Reconstitution: SW.[2–4]

Antihemophilic Factor (Human)

Maximum concentration	None.
Preparation and delivery	Allow product to come to room temperature before reconstitution. Use transfer needle provided or syringe and needle to transfer diluent into vial of drug. Gently agitate or rotate vial after addition of diluent. Do not vigorously shake vial. Do not refrigerate after reconstitution, administer within 3 hours after reconstitution.[1–4] Use plastic syringes; proteins may adhere more to glass syringes.[1–4] Hemofil M and Monoclate P have been demonstrated to be stable at room temperature and retain activity above 80% for at least 24 hours after reconstitution.[9]
IV push	Hemofil M may be administered at a maximum rate of 10 mL/min.[2] Monoclate-P may be administered at a maximum rate of 2 mL/min.[3] Koāte-DVI may be administered over 5–10 minutes; adjust administration rate based on patient response.[4]
Intermittent infusion	No recommendation.
Continuous infusion	Continuous infusion has been used in the treatment of moderate and severe bleeds in hemophilia. It has been shown that using a continuous infusion of factor after initial homeostasis is achieved can result in less overall factor consumption by avoiding the peaks and troughs associated with bolus dosing.[10–13] It appears that adjusted-dose continuous infusion, where the dose is increased or decreased to meet a target steady-state factor level, may be preferred over fixed-dose continuous infusion.[12] **Fixed-dose continuous infusion:** Initial bolus of 25–50 International Units/kg, followed by 2–4 International Units/kg/hr to maintain activity of 50% to 100%.[12–15] **Adjusted-dose continuous infusion:** Initial bolus of 25–50 International Units/kg followed by infusion of 2–5 International Units/kg/hr to maintain Factor VIII levels as below[14,16]: **At start of surgery:** 0.7–1 International Units/mL. **Postoperative days 1–3 (steady-state):** 0.5–1 International Units/mL. **Postoperative days 4–7 (steady-state):** 0.4–0.8 International Units/mL.
Other routes of administration	Not recommended.
Comments	**Inhibitor development:** Patients with mild hemophilia appear to be at greater risk of inhibitor development after treatment with recombinant factor products (e.g. Advate, Helixate FS, Kogenate FS, Recombinate).[17,18] Continuous infusion of Factor VIII does not seem to induce inhibitor formation, although this remains controversial.[14,19]

Antihemophilic Factor (Recombinant)

Brand names

Advate, Helixate FS, Kogenate FS, Recombinate, ReFacto, Xyntha, Xyntha Solofuse

Medication error potential

Factor VIII may be confused with Factor XIII.[1]

Contraindications and warnings

Contraindications: Hypersensitivity or intolerance to any component in the product.[1–7]

Product-specific contraindications

Advate, Helixate FS, Kogenate FS: Hypersensitivity to mouse or hamster protein.[1–4]

Recombinate, ReFacto: Hypersensitivity to mouse, hamster or bovine protein.[1,5]

Other warnings: Recombinate contains latex in product packaging: avoid use in patients with latex allergy.[1,5] All brands contain polysorbate 80, which may cause allergic reactions in susceptible individuals, especially neonates.[1]

Patients treated with antihemophilic factor (AHF) products should be carefully monitored for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of these products, predominantly in previously untreated and minimally treated patients. The risk of developing inhibitors is highest during the first 20 exposure days. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures Factor VIII inhibitor concentration should be performed.

Infusion-related cautions

All products have been associated with anaphylaxis-type reactions. Reduce infusion rate or temporarily discontinue if patient experiences tachycardia or allergic-type reaction.[1–7]

Dosage

Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment: For every 1 International Unit/kg body weight of product administered, Factor VIII level should increase by 2%; calculated dose should be adjusted to the actual vial size.[1–7]

Formula to calculate dosage required, based on desired increase in Factor VIII (% of normal) *(Note: This formula assumes that the patient's baseline AHF level is <1%): International Units required = body weight (kg) × 0.5 × desired increase in Factor VIII (International Units/dL or % of normal).*[1–7]

Consult individual product labeling for specific dosing recommendations.[2–7]

Minor hemorrhage (required peak postinfusion AHF level: 20% to 40%): 10–20 International Units/kg; repeat q 12–24 hr for 1–3 days until bleeding is resolved or healing is achieved.

Moderate hemorrhage (required peak postinfusion AHF level: 30% to 60%): 15–30 International Units/kg; repeat q 12–24 hr for 3–4 days until pain and disability are resolved.

Severe/life-threatening hemorrhage

Helixate FS, Kogenate FS (required peak postinfusion AHF level, 80% to 100%): Initial, 40–50 International Units/kg; maintenance, 20–25 International Units/kg q 8–12 hr until bleeding is resolved.[3,4]

Advate, Recombinate, ReFacto, Xyntha (required peak postinfusion AHF level, 60% to 100%): 30–50 International Units/kg; repeat q 8–12 hr until threat is resolved.[1,2,5–7]

Minor surgery (required peak postinfusion AHF level, 30% to 80%): 15–40 International Units/kg; dose depends on procedure and specific product recommendations. For some procedures, a single dose plus oral antifibrinolytic therapy within 1 hour is sufficient; other procedures may require repeated doses q 12–24 hr until bleeding is resolved.

Antihemophilic Factor (Recombinant)

Dosage (cont.)	**Major surgery** **Advate (required peak pre- and postsurgery AHF level, 80% to 100%):** 40–60 International Units/kg; repeat q 8–24 hr depending on state of healing.[2] **Helixate FS, Kogenate FS (required peak pre- and postsurgery AHF level, 100%):** 50 International Units/kg; repeat q 6–12 hr initially and until healing complete (10–14 days).[3,4] **Recombinate, ReFacto (required peak pre- and postsurgery AHF level, 80% to 100%):** 40–50 International Units/kg; repeat q 8–24 hr depending on state of healing.[1,5] **Xyntha (required peak pre- and postsurgery AHF level, 60% to 100%):** 30–50 International Units/kg; repeat q 8–24 hr depending on state of healing.[6,7] **Prophylaxis (may be given on a regular schedule to prevent bleeding)** **Joint bleeding prophylaxis:** No pre-existing joint damage. **Helixate FS, Kogenate FS:** 25 International Units/kg every other day.[3,4]
Dosage adjustment in organ dysfunction	No dosage adjustment required.[2–7]
Maximum dosage	None reported.
Additives	All products contain polysorbate-80.[2–7] **Advate:** Mannitol, histidine, calcium, glutathione, von Willebrand factor.[2] **Helixate FS, Kogenate FS:** Sucrose, glycine, histidine, calcium chloride, sodium, imidazole, and copper.[3,4] **Recombinate:** Albumin, calcium, polyethylene glycol, histidine, von Willebrand factor.[5] **ReFacto, Xyntha:** Sodium chloride, sucrose, L-histidine, and calcium chloride.[1,6,7]
Suitable diluents	**Reconstitution:** Sterile water for injection.[8] Some studies have used NS and or D5W for dilution of Factor VIII to 25 units/mL with loss up to 70% Factor VIII activity.[9] Kogenate FS diluted with NS or lactated Ringer's to 120, 80 or 50 units/mL had the same relative stability, and initial dilution in NS to 80 units/mL resulted in 10% to 20% Factor VIII loss, and a further 25% to 30% loss over 72 hours.[10] However, this does not appear to affect hemostatic efficacy or clinical outcome in patients treated with continuous infusions of Factor VIII.[10,11]
Maximum concentration	None reported.
Preparation and delivery	Allow product to come to room temperature before reconstitution. Use transfer needle provided or syringe and needle to transfer diluent into vial of drug. Gently agitate or rotate vial after addition of diluent. Do not vigorously shake vial, do not refrigerate after reconstitution, and administer within 3 hours after reconstitution.[1,8] Use plastic syringes; proteins may adhere more to glass syringes.[8]

Antihemophilic Factor (Recombinant)

Preparation and delivery *(cont.)*	Stable at room temperature and retains activity above 80% for at least 24 hours after reconstitution.[12,13] Because it is a poor microbial growth media, once prepared under aseptic technique, recombinant Factor VIII can be reconstituted and infused continuously for up to 3 days without risk of sepsis.[14]
IV push	Total dose may be administered over 5–10 minutes. Maximum rate of infusion 10 mL/min.[1] Advate may be administered over ≤5 minutes.[2] Helixate FS and Kogenate FS may be administered over 1–15 minutes.[3,4]
Intermittent infusion	Not reported.
Continuous infusion	Continuous infusion has been used in the treatment of moderate and severe bleeds in hemophilia. It has been shown that using a continuous infusion of factor after initial homeostasis is achieved can result in less overall factor consumption by avoiding the peaks and troughs associated with bolus dosing.[15-17] It appears that adjusted-dose continuous infusion, where the dose is increased or decreased to meet a target steady-state factor level, may be preferred over fixed-dose continuous infusion.[17] **Fixed-dose continuous infusion:** Initial bolus of 25–50 International Units/kg, followed by 2–4 International Units/kg/hr to maintain activity of 50% to 100%.[17–20] **Adjusted-dose continuous infusion:** Initial bolus of 25–50 International Units/kg followed by infusion of 2–5 International Units/kg/hr to maintain Factor VIII levels as below[18]: **At start of surgery:** 0.7–1 International Units/mL. **Postoperative days 1–3 (steady-state):** 0.5–1 International Units/mL. **Postoperative days 4–7 (steady-state):** 0.4–0.8 International Units/mL.
Other routes of administration	Not recommended.
Comments	**Inhibitor development:** Patients with mild hemophilia appear to be at greater risk of inhibitor development after treatment with recombinant factor products.[21,22] Continuous infusion of Factor VIII does not seem to induce inhibitor formation, although this remains controversial.[18,23]

Antihemophilic Factor/von Willebrand Factor Complex (Human)

(Factor VIII Complex)

Brand names	Alphante, Humate-P, Wilate
Medication error potential	Factor VIII may be confused with Factor XIII.[1]
Contraindications and warnings	**Contraindications:** Hypersensitivity or intolerance to any component in the product.[1–4] **Other warnings:** Alphanate and Wilate contain polysorbate 80, which may cause allergic reactions in susceptible individuals, especially neonates.[2,4] Human antihemophilic factor (AHF) products are prepared from human pooled plasma and may carry a risk for transmission of infectious agents, despite viral attenuation processes.[2–6] Hepatitis A and B vaccination are recommended in all hemophilia patients.[5] Thromboembolic events have been reported in von Willebrand patients receiving AHF/von Willebrand factor complex, especially in cases of other known thromboembolic risk factors and in females: use caution in these patients.[1–4] Massive doses of AHF/von Willebrand factor complex have been associated with a few cases of acute hemolytic anemia, increased bleeding tendency or hyperfibrinogenemia, which resolve upon discontinuation of the product.[7] Alphanate and Humate P contain blood group specific isoagglutinins and patients with blood groups A, B, or AB who receive large or frequent doses should be monitored for signs on intravascular hemolysis and decreasing hematocrit and treated appropriately.[2–3] Patients treated with AHF products should be carefully monitored for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of these products, predominantly children <5 years of age. The risk of developing inhibitors is highest during the first 20 exposure days. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures Factor VIII inhibitor concentration should be performed. Patients with von Willebrand disease (vWD), especially type 3, may potentially develop inhibitors to von Willebrand factor. Since inhibitor antibodies may occur concomitantly with anaphylactic reactions, patients with anaphylactic reactions should be evaluated for the presence of inhibitors.[1–4]
Infusion-related cautions	All products have been associated with anaphylaxis-type reactions. Reduce infusion rate or temporarily discontinue if patient experiences tachycardia or allergic-type reaction.[1–4]
Dosage	**Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment.** **Hemophilia A:** For every 1 International Unit/kg body weight of product administered, Factor VIII level should increase by 2 International Units/dL or 2%; calculated dose should be adjusted to the actual vial size.[1–3] Formula to calculate dosage required, based on desired increase in Factor VIII (% of normal). **Note:** This formula assumes that the patient's baseline AHF level is <1%: International Units required = body weight kg) × 0.5 × desired increase in Factor VIII (International Units/dL or % of normal).[1–3]

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Dosage *(cont.)*

Consult individual product labeling for specific dosing recommendations.[2–3]

Minor hemorrhage: Loading dose, FVIII:C 15 International Units/kg to achieve FVIII:C levels to 30% of normal. One infusion may be sufficient.

Alphanate: 15 International Units Factor VIII/kg q 12 hr until hemorrhage stops and healing has been achieved (about 1–2 days).[2]

Humate P: 7.5 International Units Factor VIII/kg q 12–24 hr until hemorrhage stops and healing has been achieved (about 1–2 days).[3]

Moderate hemorrhage: Loading dose, FVIII:C 25 International Units/kg to achieve FVIII:C levels to 50% of normal.

Alphanate: 25 International Units Factor VIII/kg q 12 hr until healing has been achieved (about 2–7 days).[2]

Humate P: 15 International Units Factor VIII/kg q 8–12 hr for first 1–2 days to maintain FVIII:C plasma level at 30% of normal. Continue 15 International Units Factor VIII/kg q 12–24 hr for up to 7 days or until healing has been achieved.[3]

Severe/life-threatening hemorrhage: Loading dose, FVIII:C 40–50 International Units/kg.

Alphanate: 40–50 International Units Factor VIII/kg q 12 hr to maintain FVIII:C levels at 80% to 100% of normal for at least 3–5 days. Then, 25 International Units Factor VIII/kg q 12 hr to maintain FVIII levels at 50% of normal until healing has been achieved. May require up to 10 days of treatment.[2]

Humate P: 20–25 International Units Factor VIII/kg q 8 hr to maintain FVIII:C plasma level at 80% to 100% of normal for 7 days. Continue 20–25 International Units Factor VIII/kg q 12–24 hr for up to 7 days to maintain the FVIII:C level at 30% to 50% of normal.[3]

Surgery

Alphanate: Preoperatively, FVIII:C levels should be increased to 80% to 100% of normal; loading dose of 40–50 International Units Factor VIII/kg. Maintain FVIII levels at 60% to 100% of normal for first 7–10 postoperative days or until healing is achieved, approximately 30–50 International Units Factor VIII/kg q 12 hr.[2]

vWD bleeding episode treatment (use Humate P product): Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment. Generally, for every 1 International Unit/kg body weight of Factor VIII administered, von Willebrand factor: Ristocetin cofactor (vWF:RCo) level should increase by about 5 International Units/dL.[3,8]

Type 1, mild (baseline vWF:RCo activity typically >30%)

Minor hemorrhage when desmopressin inadequate or major hemorrhage: Loading dose of 40–50 International Units/kg, followed by 40–50 International Units/kg q 8–12 hr for 3 days to maintain trough vWF:RCo >50%. Then, 40–50 International Units/kg q 24 hr for up to 7 days.[3]

Type I, moderate or severe (baseline vWF:RCo activity typically <30%)

Minor hemorrhage: 40–50 International Units/kg for 1–2 doses.

Major hemorrhage: Loading dose of 50–75 International Units/kg, followed by 40–60 International Units/kg q 8–12 hr for 3 days to maintain trough vWF:RCo >50%. Then, 40–60 International Units/kg q 24 hr for up to 7 days.[3]

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Dosage *(cont.)*

Type 2 (all variants) and Type 3

Minor hemorrhage: 40–50 International Units/kg for 1–2 doses.

Major hemorrhage: Loading dose of 60–80 International Units/kg, followed by 40–60 International Units/kg q 8–12 hr for 3 days to maintain trough vWF:RCo >50%. Then, 40–60 International Units/kg q 24 hr for up to 7 days.[3]

vWD minor and major hemorrhage (use Wilate product)[4,9]

Minor hemorrhages: Loading dose of 20–40 International Units/kg. Maintenance 20–30 International Units/kg q 12–24 hr for up to 3 days to maintain vWF:RCo and Factor VIII activity trough levels of >30%.

Major hemorrhages: Loading dose of 40–60 International Units/kg. Maintenance 20–40 International Units/kg q 12–24 hr for up to 5–7 days to maintain vWF:RCo and Factor VIII activity trough levels >50%.

vWD surgery/procedure prophylaxis (except Type 3 undergoing major surgery) (use Alphanate product): Individualize dosage based on coagulation studies performed prior to treatment and at regular intervals during treatment. Target FVIII:C level 40–50 International Units/dL for minor surgery and 100 International Units/dL for major surgery.[2,8]

Children

Preoperative dose: 75 International Units/kg.

Maintenance dose: 50–75 International Units/kg q 8–12 hr PRN clinically for 1–3 days.

Adults

Preoperative dose: 60 International Units/kg.

Maintenance dose: 40–60 International Units/kg q 8–12 hr PRN clinically for 1–3 days.

vWD surgery/procedure prevention of bleeding (use Humate P product): The in vivo recovery (IVR) should be measured and baseline plasma vWF:RCo and FVIII:C should be assessed in all patients prior to surgery. The IVR is calculated by measuring baseline plasma vWF:RCo; then infuse vWF/RCo 60 International Units/kg IV at time zero; measure vWF:RCo at 30 minutes after infusion. The IVR = (plasma vWF:RCo at 30 minutes minus plasma vWF:RCo at baseline) divided by 60 International Units/kg. A standardized loading dose may be used when individual IVR is not available; based on assumed IVR of 2 International Units/dL for every 1 vWF:RCo International Unit/kg administered.[3,8]

Emergency surgery: Administer vWF:RCo 50–60 International Units/kg; monitor trough coagulation factor levels to determine subsequent doses.

Surgery (nonemergency): Loading dose based on baseline target vWF:RCo: International Units vWF:RCo required = (Target peak vWF:RCo minus Baseline vWF:RCo) × weight (kg)/IVR. Loading dose should be administered 1–2 hours prior to surgery/procedure.

Target concentrations for vWF:RCo after loading dose

Minor surgery: 50–60 International Units/dL.

Major surgery: 100 International Units/dL.

Antihemophilic Factor/von Willebrand Factor Complex (Human)

Dosage *(cont.)*	**Maintenance dose:** 50% of loading dose followed by dosing determined by target trough concentrations; usually administered q 8–12 hr.[1,3] **Target maintenance trough vWF:RCo levels** **Oral surgery:** ≥30 International Units/dL for minimum duration of 8–12 hr. **Minor surgery:** ≥30 International Units/dL for minimum duration of 48 hr. **Major surgery:** ≥50 International Units/dL for up to 3 days; followed by >30 International Units/dL for minimum of 72 hours total treatment. **Prophylaxis of bleeding episodes:** May be administered on a regular schedule to prevent bleeding in Hemophilia A and vWD, usually 2–3 times weekly. Dose should be individualized based on age, venous access, activity and availability of clotting factor concentrates.[9–12] In a recent study, 17 children and adolescents as well as 12 *adults* with vWD (types 1–3) received Humate P or Wilate at a median dose of 40 International Units/kg based on vWF:RCo activity baseline and 24-hour trough levels. Patients received infusions between 2 and 4 times per week. Within 1 year, hemoglobin concentrations returned to normal values and recurrent bleeding ceased in 31 of 32 patients.[11]
Dosage adjustment in organ dysfunction	No dosage adjustment required.[1–4]
Maximum dosage	None reported.
Additives	**Alphanate:** Albumin, calcium, glycine, heparin (≤1 unit/mL), histidine, imidazole, arginine, polyethylene glycol, polysorbate 80, sodium, tri-n-butyl phosphate.[2] **Humate P:** Albumin, glycine, sodium citrate, sodium chloride, fibrinogen (≤0.2 mg/mL).[3] **Wilate:** Glycine, sucrose, sodium chloride, sodium citrate, calcium chloride, polysorbate 80.[4]
Suitable diluents	**Reconstitution:** SW.[2–4]
Maximum concentration	None.
Preparation and delivery	Allow product to come to room temperature before reconstitution. Use transfer needle provided or syringe and needle to transfer diluent into vial of drug. Gently agitate or rotate vial after addition of diluent. Do not vigorously shake vial. Do not refrigerate after reconstitution, administer within 3 hours after reconstitution.[1–4] Use plastic syringes; proteins may adhere more to glass syringes.[2–4] Humate-P was found to be stable for 14 days at room temperature after reconstitution per manufacturer directions in a study by Lubetsky.[13] Mean vWF:RCo assay was 64.3 ± 4.9 International Units/mL following reconstitution and 53.0 ± 7.0 International Units/mL at day 14 in the presence or absence of heparin (4 units/mL of factor concentrate).[13]

Antihemophilic Factor/von Willebrand Factor Complex (Human)

IV push	Alphanate should be administered at a maximum rate of 10 mL/min.[2] Humate P should be administered at a maximum rate of 4 mL/min.[3] Wilate should be administered at a maximum rate of 2–4 mL/min.[4]
Intermittent infusion	No information.
Continuous infusion	Continuous infusion has been used in the treatment of moderate and severe bleeds in hemophilia as well as in limited studies in vWD. It has been shown that using a continuous infusion of factor after initial homeostasis is achieved can result in less overall factor consumption by avoiding the peaks and troughs associated with bolus dosing.[13–18] Humate-P was reconstituted and administered via minipump with added heparin (4 units/mL of factor concentrate) in 8 patients with mild-to-severe vWD. Initial bolus dose and rate of infusion were determined by pharmacokinetic evaluation and adjusted to maintain vWF:RCo levels of 0.5–0.7 International Units/mL during the first days of treatment. Rate of infusion was adjusted daily per ristocetin cofactor clearance. Treatment with continuous Humate-P was effective in stopping bleeding episodes or preventing bleeding during or after surgical interventions.[13]
Other routes of administration	Not recommended.
Comments	The ratio of VWF:RCo to FVIII in Alphanate varies by lot; check International Units VWF:RCo/vial to ensure accurate dosing.[2]

Anti-inhibitor Factor Complex

Brand names	Feiba NF
Medication error potential	None reported.
Contraindications and warnings	**Contraindications:** Hypersensitivity or intolerance to any component in the product, in patients with normal coagulation mechanism, significant signs of disseminated intravascular coagulation, acute thrombosis or embolism (including myocardial infarction), and in the treatment of bleeding episodes from coagulation factor deficiencies without the presence of inhibitors to coagulation Factor VIII or IX.[1] **Precautions:** Use with caution in patients with increased risk for thrombotic risk factors (e.g., history of congenital heart disease, liver disease, disseminated intravascular coagulation, postoperative immobilization, neonates and elderly patients). If signs of intravascular coagulation occur, including changes in blood pressure, pulse rate, respiratory distress, chest pain and/or cough, stop the infusion and institute appropriate diagnostic and therapeutic measures.[1] Do not use systemic antifibrinolytics such as tranexamic acid or aminocaproic acid, within 12 hours of Feiba NF dosing.[1] **Other warnings:** The 50-mL provided diluent (SW) stoppers are not latex free and may contain dry natural rubber latex.[1]
Infusion-related cautions	May precipitate allergic-type hypersensitivity reactions, which may be severe. Other infusion-related reactions such as chills, fever, and hypertension have been reported.[1]
Dosage	*Dosage depends on the severity and location of bleeding, types and levels of inhibitors, and whether there is a history of an anamnestic increase in antihemophilic factor (AHF) after use of preparations containing AHF.*[1,2] **Treatment of bleeding/hemorrhage:** Considered first-line treatment for control of spontaneous bleeding episodes or for surgical interventions in patients with Factor VIII inhibitor titers of >5 Bethesda units (BU).[1–5] **General dosing:** 50–100 units/kg; dosage may vary with bleeding site and severity (maximum dose 200 units/kg/day). **Joint hemorrhage:** 50 units/kg q 12 hr; may increase to 100 units/kg q 12 hr (maximum dose 200 units/kg/day). **Mucous membrane bleeding:** 50 units/kg q 6 hr; may increase to 100 units/kg q 6 hr for up to 2 doses (maximum dose 200 units/kg/day). **Soft tissue hemorrhage:** 100 units/kg q 12 hr (maximum dose 200 units/kg/day). **Other severe hemorrhages:** 100 units/kg q 12 hr; dosing interval may be shortened to q 6 hr if needed (maximum dose 200 units/kg/day). **Prophylaxis of bleeding:** 50–100 units/kg IV on three, nonconsecutive days per week.[6–10] In a case report, a patient with hemophilia A and Factor VIII inhibitor of 8 BU/mL received 50 units/kg Feiba 3 times weekly at home by IV infusion over 30 minutes. Over 24 months of follow-up, no bleeding or thrombotic events were reported and inhibitor levels decreased to 1 BU/mL.[11] **Surgical prophylaxis**[5,12] **Major surgical procedures:** 50–100 units/kg prior to surgery followed by infusions q 6–12 hr to maximum dose of 200 units/kg/day. **Minor surgical procedures:** 50–100 units/kg prior to surgery, followed by daily infusions for 1–5 days.

Anti-inhibitor Factor Complex

Dosage adjustment in organ dysfunction	No dosage adjustment required.[1]
Maximum dosage	Doses above 200 units/kg/day have been associated with thrombotic and thromboembolic events.[1]
Additives	Each mL of reconstituted product contains 4 mg trisodium citrate and 8 mg sodium chloride.[1]
Suitable diluents	Sterile water for injection. Use provided diluent.[1]
Maximum concentration	None reported.
Preparation and delivery	Allow product and provided diluent to come to room temperature before reconstitution. Gently swirl to make sure that product is completely dissolved.[1] Do not refrigerate after reconstitution. Use within 3 hours after reconstitution. Do not further dilute.[1] Plastic Luer lock syringes should be used if needed; proteins in the product may stick to the surface of all-glass syringes.[1]
IV push	Maximum injection rate should not exceed 2 units/kg/min.[1]
Intermittent infusion	Maximum rate should not exceed 2 units/kg/min.[1]
Continuous infusion	Not reported.
Other routes of administration	Not recommended.
Comments	Do not mix or administer Feiba NF with other medicinal products or solvents.[1] If anticipated treatment responses are not achieved, obtain platelet count. A sufficient number of functionally intact platelets are necessary for the product to be effective.[1]

Argatroban

Brand names	Generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP and USP report that argatroban has been confused with Aggrastat; no patient harm resulted.[2,3] ISMP also reports that argatroban has been confused with Orgaran.[2]
Contraindications and warnings	Use with caution in patients with diseases that have an increased risk for hemorrhage.[4] All parenteral anticoagulants should be discontinued before use of argatroban.[4]
Infusion-related cautions	Allergic reactions have been reported, and they were primarily in patients receiving other antithrombotic therapy or contrast media.[4]
Dosage	*See Dosing Adjustment in Organ Dysfunction section for initial dosing suggestions in patients with hepatic impairment.* **Dosing adjustment for obesity:** One retrospective trial in *adults* receiving infusions for prophylaxis or treatment of thrombosis found that activated partial thromboplastin time (aPTT) responses were not different between obese (BMI >30 kg/m^2) and nonobese patients, and that infusions of 1 mcg/kg/min provided therapeutic aPTTs.[5] **Infants and children**[4,6–10] **Prophylaxis or treatment of thrombosis, treatment of heparin-induced thrombocytopenia (HIT) or suspected HIT:** 0.75 mcg/kg/min initially, then titrated in increments of 0.1–0.25 mcg/kg/min to goal aPTT of 1.5–3 × baseline (not to exceed 100 seconds).[4,9,10] Infusion rates have ranged from 0.1–13 mcg/kg/min.[7,10] **Extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD):** A multicenter study used the following protocol: circuit prime of 50 mcg/750 mL, initial bolus of 100 mcg/kg, initial infusion of 2 mcg/kg/min titrated to activated clotting time (ACT) 180–220 seconds.[10] A review reported that 12 patients received varying regimens; infusions ranged from 0.1–24 mcg/kg/min (usually <6 mcg/kg/min).[7] **Hemodialysis or continuous venovenous hemofiltration (CVVH):** A multicenter study used the following protocol: initial bolus of 250 mcg/kg and initial infusion of 2 mcg/kg/min titrated to ACT 180–220 seconds.[10] A review reported that five patients on hemodialysis received infusions of 0.1–2 mcg/kg/min (one received an initial bolus of 65 mcg/kg).[7] **Cardiac catheterization:** A multicenter study used the following protocol: bolus of 250 mcg/kg and initial infusion of 15 mcg/kg/min titrated to ACT 200–300 seconds.[10] A review reported that five patients received a bolus of 150 or 250 mcg/kg followed by infusion rates of 7.5–15 mcg/kg/min titrated to an ACT of 300.[7] **Cardiopulmonary bypass:** A 2.5-month-old infant received 2–5 mcg/kg/min with boluses of 20 mcg/kg PRN to achieve ACT ≥400 seconds. No loading dose or pump prime was used.[6] A multicenter study used the following protocol: circuit prime of 50 mcg/750 mL, loading dose of 250 mcg/kg, and initial infusion of 20 mcg/kg/min titrated to ACT 400–500 seconds.[10] ***Adults* with HIT and HIT with thrombosis syndrome (HITTS)**[4] **Prophylaxis or treatment of thrombosis:** 2 mcg/kg/min with the infusion adjusted up to 10 mcg/kg/min to steady-state aPTT of 1.5–3 × baseline value (≤100 seconds). **Percutaneous coronary intervention (PCI):** Bolus 350 mcg/kg via large bore IV line over 3–5 minutes followed by infusion of 25 mcg/kg/min. Titrate to goal ACT (refer to package insert for full recommendations).

Dosage adjustment in organ dysfunction	No dosage adjustment is needed for impaired renal function.[4] **Impaired hepatic function (defined in one study as aspartate aminotransaminase/alanine transaminase [AST/ALT] ≥3 × upper limit of normal)**[10] **Prevention or treatment of thrombosis:** 0.2 mcg/kg/min initially titrated to aPTT of 1.5–3 × baseline making incremental changes of ≤0.05 mcg/kg/min.[4,10] **Cardiopulmonary bypass**[10]**:** Circuit prime of 50 mcg/750 mL, initial bolus of 62.5 mcg/kg, initial infusion of 5 mcg/kg/min titrated to ACT 400–500 seconds. **Cardiac catheterization**[10]**:** Initial bolus of 62.5 mcg/kg, initial infusion of 3.75 mcg/kg/min titrated to ACT 200–300 seconds. **ECMO or VAD**[10]**:** Circuit prime of 50 mcg/750 mL, initial bolus of 25 mcg/kg, initial infusion of 0.5 mcg/kg/min titrated to ACT 180–220 seconds. **Hemodialysis or CVVH**[10]**:** Initial bolus of 62.5 mcg/kg, initial infusion of 0.5 mcg/kg/min titrated to ACT 180–220 seconds.
Maximum dosage	In *adults,* 10 mcg/kg/min for HIT or 40 mcg/kg/min for PCI to maintain an ACT of 300–450 seconds.[4] A 5-month-old required 15 mcg/kg/min to reach a target ACT of 300 seconds during cardiac catheterization.[7] A 15-month-old on ECMO required 24 mcg/kg/min to attain an aPTT 2 × baseline; the rate subsequently stabilized at 13–15 mcg/kg/min.[11]
Additives	None.
Suitable diluents	NS, D5W, LR.[4,12]
Maximum concentration	1 mg/mL.[4,12]
Preparation and delivery	The IV solution may appear hazy after dilution. The solution should clear with continued mixing.[4,12]
IV push	Over 3–5 minutes (bolus dose in *adults*).[4]
Intermittent infusion	Infused for the duration of PCI or cardiac catheterization.[4]
Continuous infusion	1 mg/mL. May be infused continuously.[4]
Other routes of administration	Not indicated.
Comments	The ninth edition of the *Antithrombotic Therapy and Prevention of Thrombosis* guidelines from the American College of Chest Physicians (ACCP) notes that danaparoid sodium, hirudin, and argatroban are alternatives to heparin in the treatment of children with HIT.[13] **Monitoring:** Goal aPTT generally 1.5–3 × baseline, not to exceed 100 seconds. Obtain aPTT 2 hours after every dose adjustment and at least once daily and as clinically indicated during treatment. Goal ACT dependent on procedure. ACT to be evaluated 5–10 minutes after each bolus completed, after the initiation of any infusion dose change, and at 1-hour intervals for cardiac catheterization or cardiac surgery or 12-hour intervals for other procedures.[10]

Arginine HCl

Brand names	R-Gene 10
Medication error potential	Overdose in children has resulted in hyperchloremic metabolic acidosis, cerebral edema, and death; hence, dosing calculations should be carefully checked prior to administration.[1]
Contraindications and warnings	In persons having known hypersensitivity to any ingredient in this product.[1] Anaphylactic reactions have been reported in two children.[2,3] Antihistamines should be available in the event an allergic reaction occurs.[1]
Infusion-related cautions	Flushing, nausea, vomiting, numbness, headache, and local venous irritation are associated with rapid infusion.[1] (See Comments section.) Extravasation, causing tissue necrosis, has been reported in three children (ages 3.5–7 years) who received a 10% solution.[4,5]

Dosage

Growth hormone reserve test (pituitary function test): 500 mg/kg not to exceed 30 g (*adult* dose = 300 mL or 30 g) over 30 minutes.[6–8] Infuse via antecubital or other suitable vein. Inadequate dosing or prolonged infusion period may diminish the stimulus to the pituitary and nullify the test.[1]

Inborn errors of urea synthesis: Arginine is given with sodium benzoate and sodium phenylacetate to treat hyperammonemia.[9–11] Monitor acid–base balance closely.

Argininosuccinic acid lyase or argininosuccinic acid synthetase deficiency: Loading dose of 600 mg/kg (12 g/m^2) infused over 90 minutes followed by 600 mg/kg/day (12 g/m^2/day) as a continuous infusion via central venous line.

Carbamyl phosphate synthetase or ornithine transcarbamylase deficiency: Loading dose of 200 mg/kg (4 g/m^2) followed by 200 mg/kg/day (4 g/m^2/day) as a continuous infusion via central venous line.

The loading dose should only be repeated in neonates with severe disorders or in those receiving dialysis. If an additional dose is given, the 2 doses should be given at least 6 hours apart.[9] (See Maximum Dosage section.)

Other uses

Necrotizing enterocolitis (NEC) (prevention): 261 mg/kg/day administered on days 2–5 of life and continued for 28 consecutive days.[12] This recommendation is based on one small, randomized controlled study in preterm neonates, which showed that arginine supplementation significantly reduced the incidence of all cases of NEC. It is not known whether the hydrochloride salt was used in this study. There continues to be insufficient evidence to recommend arginine supplementation for infants at risk for NEC.[13]

Severe hypochloremia: Arginine hydrochloride dose (mEq) = 0.2 × weight (kg) × [103 – patient's serum chloride (mEq/L)].[14] Give 50% to 75% of estimated dose and reassess serum chloride.

Severe metabolic alkalosis: Arginine should be used only after sodium and potassium chloride supplementation has failed (serum pH >7.55).[15] Two approaches are commonly used to estimate dosage:

Arginine dose (g) = [desired decrease in plasma bicarbonate (mEq/L) × weight (kg)] ÷ 9.6.[15]

or

Arginine dose (mEq) = 0.5 × weight (kg) × [patients plasma bicarbonate (mEq/L) – 24].[14]

Give 50% to 75% of estimated dose and reassess plasma bicarbonate.

Pulmonary hypertension: 500 mg/kg over 30 minutes.[16–18]

Dosage adjustment in organ dysfunction	Patients with renal and hepatic insufficiency may accumulate arginine.[1] Arginine is metabolized to nitrogen-containing products that are renally eliminated; hence, accumulation of arginine may result in an overproduction of nitric oxide, leading to vasodilation and hypotension.[1]
Maximum dosage	60 g/hr (285 mEq/hr); 1 g/kg/hr (4.75 mEq/kg/hr).[19]
Additives	Contains 0.475 mEq/mL of chloride. Each 1 mEq chloride delivers 1 mEq hydrogen.[1] (See Comments section.)
Suitable diluents	D10W.[1]
Maximum concentration	100 mg/mL (commercially available).[1] Because the solution is hypertonic (950 mOsm/L) it should only be given via a secure IV line.[1]
Preparation and delivery	**Preparation:** For pediatric patients weighing <60 kg, withdraw a weight-based dose from a sealed R-Gene 10 bottle and place in a separate container for IV infusion. This should avoid the inadvertent delivery and administration of the total volume from the commercially available container.[1] The dose (600 mg/kg) can be diluted in 25–35 mL D10W.[20] **Delivery system issues:** Stable in polypropylene syringes and plastic containers made of either PVC or EVA.[1] **Compatibility:** Compatible with sodium phenylacetate and sodium benzoate.[1] **Stability:** Store at room temperature (25°C).[1] Postpenetration storage (including infusion time) should not exceed 4 or 24 hours at room (25°C) or refrigerated (2°C to 8°C) temperatures, respectively.[1] Inspect solution prior to administration and discard if it is not clear.
IV push	Not recommended. (See Infusion-Related Cautions section.)
Intermittent infusion	Over 30 minutes for growth hormone reserve test[1] and over 90–120 minutes for inborn errors of metabolism.[1,9,18]
Continuous infusion	Used for treatment of inborn errors of urea synthesis and hyperammonemia.[1]
Other routes of administration	Not indicated due to hypertonicity.[1]
Comments	**Hyperkalemia:** Because of the high chloride content, those with electrolyte abnormalities may experience hyperkalemia. Two patients with severe hepatic disease and moderate renal insufficiency developed hyperkalemia following treatment for metabolic alkalosis with L-arginine.[21] Despite aggressive treatment, one of these died.[21] Four *adults* with chronic renal failure on hemodialysis underwent an evaluation of growth hormone metabolism and developed significant hyperkalemia.[22] Those being treated for hyperammonemia may experience hyperchloremic metabolic acidosis. Serum concentrations of chloride and bicarbonate should be monitored to determine the need for bicarbonate therapy. **Hypotension:** Decrease in blood pressure was noted within 10 minutes of drug administration in 11 children (9.4 ± 4.1 years) receiving 500 mg/kg of arginine for pituitary function testing. Blood pressure returned to normal within 30 minutes.[8] **Overdose:** A 21-month-old girl inadvertently received 3.9 g/kg (300 mL of 10% arginine) over 30 minutes.[23] She experienced gasping respirations and immediate cardiopulmonary arrest with acute metabolic acidosis and transient hyponatremia. Thirty-six hours later, she experienced fatal central pontine and extrapontine myelinolysis. At 750 mg/kg/24 hr, a patient may experience vomiting and lethargy, and doses >750 mg/kg/24 hr can be life-threatening.[9]

Asparaginase

Brand names	Elspar ***Note: Elspar (asparaginase) was discontinued as of December 31, 2012.***
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that asparaginase has been confused with pegaspargase; no patient harm resulted.[2] USP also reports that Elspar has been confused with Oncaspar; no patient harm resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** Asparaginase should be administered under the supervision of an experienced physician. The drug is highly toxic; special handling precautions should be in place.[3,4] **Contraindications:** Asparaginase is contraindicated in patients with serious allergic reactions to asparaginase or other *E-coli*-derived L-asparaginases and serious thrombosis, pancreatitis, or serious hemorrhagic event with previous asparaginase use.[3] **Other warnings:** Asparaginase carries a warning about the severity and incidence of anaphylaxis.[3] The following administration parameters are associated with an increased risk of hypersensitivity reactions: IV administration, dosages >6000–12,000 units/m^2, previous regimens containing asparaginase, and intermittent therapy.[4] Asparaginase has also been associated with coagulopathy, hyperglycemia, pancreatitis, hepatic dysfunction, tumor lysis syndrome, and thrombosis.[3,4]
Infusion-related cautions	Has been associated with serious anaphylaxis.[3] (See Contraindications and Warnings section.) When administering asparaginase, emergency treatment (including IV diphenhydramine, epinephrine, and hydrocortisone with a freely running IV in place) should be available.[4] Patients should be monitored for 1 hour following administration and the drug should not be administered at night.[4]
Dosage	Consult individual protocol for complete dosing information. Asparaginase is used as a component of combination therapy to treat childhood acute lymphocytic leukemia.[3] To reduce the incidence of adverse effects, asparaginase should be administered after other chemotherapeutic agents, specifically vincristine and prednisone. **Test dose:** Hypersensitivity reactions commonly occur and intradermal testing is recommended in all patients prior to asparaginase therapy.[4] Inject 0.1 mL of a solution of 20 units/mL (2 units) intradermally and observe injection site for 1 hour.[4] A wheal or erythema represents a positive reaction; false–negative reactions may occur.[4] Patients with a positive skin test may undergo desensitization therapy if the benefits of therapy outweigh the risks. One desensitization protocol recommends 1 unit of asparaginase IV that is doubled q 10 min until the total amount of the daily total dosage has been met (provided no adverse events occur).[4] **Induction therapy (combination therapy)** **IV:** 1000 units/kg/day for 10 days or 6000 units/m^2/dose 3 times per week for 6–9 doses.[4] **IM:** 6000–10,000 units/m^2/dose given every third day for 3 weeks.[3,4,7,8] A high dose of 25,000 units/m^2 has also been administered once weekly for 9 weeks.[9] **Induction therapy (monotherapy—not recommended if patient can tolerate combination therapy):** 200 units/kg/day for 28 days.[4,10] **Maintenance therapy:** Not recommended.[3]

Asparaginase

Dosage adjustment in organ dysfunction	Asparaginase has been associated with hepatic dysfunction. However, no dosage adjustments have been recommended with any pre-existing organ dysfunction, including hepatic.[3]
Maximum dosage	Not established.
Additives	80 mg of mannitol in lypophilized form.[3]
Suitable diluents	Reconstitute with SW, NS; further dilute during administration with a running IV of D5W or NS.[3,11]
Maximum concentration	2000 units/mL (IV) and 5000 units/mL (IM).[3,11]
Preparation and delivery	**For IV administration:** The volume recommended for reconstitution is 5-mL suitable diluent to the 10,000-unit vial. Ordinary shaking during reconstitution does not inactivate the enzyme.[3] **For IM administration:** The volume recommended for reconstitution is 2-mL NS to the 10,000-unit vial.[3] Use within 8 hours and only if solution is clear.[3] Gelatinous fiber-like particles may develop after reconstitution; administration with a 5-micron filter will remove any particles without loss of potency.[3] When handling asparaginase (during preparation and administration), avoid inhaling aerosols or dust or contact with the mucous membranes or skin.[3]
IV push	Not recommended.[3,11]
Intermittent infusion	Administer over at least 30 minutes with a running infusion of D5W or NS.[3,11]
Continuous infusion	Intermittent infusion or IM administration are preferred routes of administration. Continuous infusions of asparaginase have been reported.[12]
Other routes of administration	May be given via IM administration. (See Preparation and Delivery section.) Do not exceed 2 mL at each injection site.[3] Two injection sites should be used if the volume of required dose is >2 mL. IM administration is associated with a lower incidence of anaphylaxis compared to IV administration.[3,13] IT and intraventricular administration of asparaginase have been reported in patients with CNS lymphoblastic leukemia.[14,15] However, these routes have not demonstrated superiority over conventional treatments.
Comments	**Monitoring:** Vital signs during administration, CBC with platelets, urinalysis, liver function, coagulation, renal function, glucose level (urine and blood), bilirubin, amylase, and uric acid.[3,4] **Drug interactions:** Use caution when administering with dexamethasone as this may increase serum levels of dexamethasone.[3,4,16]

Asparaginase–Pegylated (Pegaspargase)

Brand names	Oncaspar
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that pegaspargase has been confused with asparaginase; no patient harm resulted.[2] USP also reports that Oncaspar has been confused with Elspar; no patient harm resulted.[2]
Contraindications and warnings	**Contraindications:** Pegaspargase is contraindicated in patients with serious allergic reactions to pegaspargase and in patients with serious thrombosis, pancreatitis, or serious hemorrhagic event with previous asparaginase therapy.[3] **Warnings:** May cause serious hypersensitivity reactions (see Infusion-Related Cautions section) coagulopathy, glucose intolerance, pancreatitis, and thrombotic events.[3,4] Discontinue therapy if pancreatitis or thrombosis occur.[3] Reversible hepatotoxicity (hyperbilirubinemia and liver enzyme elevation) may occur.[4]
Infusion-related cautions	May cause anaphylaxis or serious allergic reactions; discontinue therapy if severe hypersensitivity occurs.[3] Due to risk of hypersensitivity reaction, IV diphenhydramine, epinephrine, hydrocortisone, and a freely running IV should be in place when administering pegaspargase.[4] Patients should be monitored for 60 minutes following administration and the drug should not be administered at night.
Dosage	Consult individual protocol for complete dosing information. Pegaspargase is used as a component of combination therapy to treat first line acute lymphocytic leukemia (ALL) and to treat ALL in patients who are hypersensitive to the native forms of L-asparaginase (Elspar).[3] It may also be used in blast crisis of chronic lymphocytic leukemia (CLL) and salvage therapy of non-Hodgkin lymphoma, although use has not been established.[4] A test dose is not required with pegaspargase as there is less risk for hypersensitivity reactions compared to L-asparaginase.[4] **Children >1 year and *adults*:** 2500 International Units/m^2/dose every 14 days.[3,4] Induction therapy with weekly doses of pegaspargase 2500 International Units/m^2 IM every 7 days, with or without intensification therapy (an additional 2500 International Units/m^2 IM dose), has also been studied, although the use of these regimens is not established.[5–7]
Dosage adjustment in organ dysfunction	Not established.
Maximum dosage	Not established. Three *adult* patients received IV infusions of 10,000 International Units/m^2 with no major adverse events.[3]
Additives	Contains 8.5 mg NaCl per mL.[3]
Suitable diluents	D5W, NS.[3]

Asparaginase–Pegylated (Pegaspargase)

Maximum concentration	Not established.
Preparation and delivery	**Preparation:** Pegaspargase may be a contact irritant. Professionals should wear gloves while handling and administering and should avoid inhalation of pegaspargase. If contact occurs with eyes, skin, or mucous membranes, wash with water for at least 15 minutes.[3,4] **Stability:** Freezing destroys the activity of pegaspargase; do not use if the product has been frozen.[3]
IV push	Not recommended.
Intermittent infusion	Administer over 1–2 hours in 100 mL of D5W or NS through an infusion already running.[3]
Continuous infusion	Not recommended.
Other routes of administration	IM administration is the preferred route of administration. Do not exceed 2 mL at each injection site. Two injection sites should be used if the volume of required dose is >2 mL.[3]
Comments	Monitor vital signs during administration, CBC with differential, platelets, urinalysis, liver function, coagulation, renal function, glucose level (urine and blood), onset of abdominal pain, serum amylase, bilirubin and uric acid concentrations.[3,4]

Atenolol

Brand names	Tenormin IV injection
Medication error potential	High-alert medication (adrenergic antagonist) associated with an increased risk of significant patient harm if an error occurs.[1] Atenolol may be confused with albuterol, Altenol, timolol, and Tylenol.[2] Tenormin may be confused with Imuran, Norpramine, thiamine, and Trovan.[2]
Contraindications and warnings	**U.S. boxed warning:** Patients with coronary artery disease should be advised against abrupt discontinuation of therapy due to reports of severe angina exacerbations and occurances of myocardial infarction and ventricluar arrhythmias.[3] **Contraindications:** Patients with pulmonary edema,[4] overt cardiac failure,[3,4] cardiogenic shock,[3,4] sinus bradycardia,[3,4] heart block greater than first degree,[3,4] or uncompensated congestive heart failure.[3,4] **Warnings:** Atenolol should not be administered to patients with untreated pheochromocytoma.[4] It is not generally used in patients with bronchospastic disease; however, when used the smallest effective dose should be given.[3] Atenolol may mask clinical signs of hyperthyroidism.[3,4] Bradycardia, heart block, and increased left ventricular end diastolic pressure can occur when administered with nondihydropyridine calcium channel blockers.[3] Beta-blockers should be used cautiously in patients with diabetes since they can mask tachycardia associated with hypoglycemia.[3] Abrupt withdrawal should be avoided; discontinue over 1–2 weeks.[3] Patients with a history of anaphylactic hypersensitivity reactions may be more reactive while receiving beta-blockers; these patients may not be responsive to the normal doses of epinephrine.[3] (See Other in the Comments section.)
Infusion-related cautions	None. (See Other in the Comments section for management of hypersensitivity reaction and bronchospasm).
Dosage	Safety and effectiveness have not been established and there is little information on IV atenolol use in pediatric patients.[3,4] 0.1 mg/kg/dose[5] up to 5 mg/dose in older adolescents and *adults*.[3] If necessary, the dose may be repeated in 10 minutes.[3,5]
Dosage adjustment in organ dysfunction	If CrCl is 30–50 mL/min/1.73/m^2, give a maximum of 1 mg/kg q 24 hr (*adult* 50 mg); if CrCl is $<$30 mL/min/1.73/m^2, give a maximum of 1 mg/kg q 48 hr.[6]
Maximum dosage	Up to 15 mg/dose have been used in *adults*.[7]
Additives	None.
Suitable diluents	D5W or NS.[8]
Maximum concentration	0.5 mg/mL (commercially available).[8]
Preparation and delivery	**Stability:** Stable for 48 hours when stored at room temperature (i.e., 20°C to 25°C).[3,8] **Photosensitivity:** Protected from light.[3,8]

IV push	Over 5 minutes,[3] not to exceed 1 mg/min.[8]
Intermittent infusion	Not given by this method.
Continuous infusion	Not given by this method.
Other routes of administration	None.
Comments	**Monitoring:** Monitor heart rate, blood pressure, and ECG during infusion.[3] **Drug interactions:** Drugs that slow atrioventricular (AV) conduction (i.e., hypotensive agents, diuretics, cardiac glycosides, amiodarone, calcium channel blockers) and depress the myocardium may have additive effects with beta-blockers. Nonsteroid anti-inflammatory drugs may decrease the antihypertensive effects of beta-blockers. Large doses of atenolol may reverse the effects of theophylline.[4] **Other:** Glucagon or ipratropium should be considered for treatment of anaphylaxis in patients receiving beta-adrenergic blocking agents.[9] A beta-2 stimulant such as isoproterenol or terbutaline and/or aminophylline may be used for the treatment of bronchospasm.[3]

Atracurium Besylate

Brand names	Tracrium, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1]
Contraindications and warnings	**Contraindications:** Patients with a hypersensitivity to atracurium or any of its components.[2] **Warnings:** Use carefully under the supervision of experienced clinicians; personnel should also be skilled in airway management and respiratory support. Intubation and ventilatory support equipment (assisted or controlled), including positive pressure oxygen, should be readily available. Reversal agents should be readily available when giving atracurium.[2]
Infusion-related cautions	Histamine release resulting in flushing, erythema, pruritus, urticaria, bronchospasm, hypotension, and changes in heart rate may occur.[2,3] Caution should be taken when administering this agent to patients who may be histamine sensitive (e.g., cardiovascular disease, previous anaphylactoid reactions, asthma).[2] Asystole has occurred in *adults*.[4]
Dosage	*Respiratory function must be supported and concurrent administration of a sedative is also necessary. Monitoring of neuromuscular transmission with a peripheral nerve stimulator is recommended during continuous infusion or with repeated dosing*.[2,5] **Dosing adjustment for obesity:** In morbidly obese *adults*, doses based on ideal body weight (0.5 mg/kg) produced effective neuromuscular blockade for ET intubation with good muscle recovery times.[6] **Dosing adjustment for hypothermic cardiac bypass:** Smaller atracurium doses (50% of usual infusion) may be required in patients undergoing hypothermia (25°C to 28°C) during cardiac bypass.[2] **Dosing adjustment during concomitant inhaled anesthetic agents:** Atracurium infusions should be reduced by 33% in patients undergoing enflurane or isoflurane anesthesia; a smaller dose reduction is required for halothane anesthesia.[2] In patients with a history of histamine sensitivity (anaphylactoid reactions or asthma), doses should be infused over 1 minute.[2] (See Infusion-Related Cautions section.) **Induction and maintenance of neuromuscular blockade** **Neonates (≤1 month)** **Initial dose:** 0.25–0.4 mg/kg.[7–10] (See Other in the Comments section.) **Maintenance dose:** 0.25 mg/kg[7] PRN. **Continuous infusion:** One study reported 0.4 mg/kg/hr (6.7 mcg/kg/min).[11] **Infants and children (1 month–2 years)** **Initial dose:** 0.3–0.5 mg/kg.[2,3,7,8,12–16] **Maintenance dose:** 0.3–0.4 mg/kg[2,7] PRN. **Continuous infusion:** 0.3–1.2 mg/kg/hr (5–20 mcg/kg/min).[3,7,11,14–17] **Children (≥2 years)** **Initial dose:** 0.3–0.5 mg/kg.[2,3,7,8,12–14,17,18] **Maintenance dose:** 0.08–0.1 mg/kg[2,7] PRN. Children may require more frequent administration than *adults*.[2]

Dosage *(cont.)*	**Continuous infusion:** 0.3–0.9 mg/kg/hr (5–15 mcg/kg/min).[2,3,7,11,14,17,19,20] Larger doses have been required to facilitate mechanical ventilation in critically ill children; mean doses were 1.6–1.72 mg/kg/hr (27–29 mcg/kg/min).[20] Infusion requirement may increase with prolonged administration.[15] (See Maximum Dosage section.)
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal[2,7,21] or hepatic dysfunction.[2,7]
Maximum dosage	0.6 mg/kg has been used safely in infants with severe hepatic dysfunction under halothane/nitrous oxide/oxygen anesthesia.[22] An infusion of 0.53 mg/kg/hr (8.8 mcg/kg/min) has been used in those >1 month of age and 0.4 mg/kg/hr (6.7 mcg/kg/min) has been given to neonates.[11] Occasionally, continuous infusion doses as large as 2.4 mg/kg/hr (40 mcg/kg/min) may be required.[14] In one study, seven pediatric patients required a mean infusion of 1.72 mg/kg/hr (28.7 mcg/kg/min) for up to 72 hours.[20] A case report described a 17-year-old who received 4.5 mg/kg/hr (75 mcg/kg/min) but experienced prolonged muscle weakness afterward.[23] (See Significant Adverse Effects in the Comments section.)
Additives	Multidose vials contain benzyl alcohol 0.9% as a preservative.[2,24] See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.
Suitable diluents	D5W, D5NS, NS. Dilution in LR results in degradation of atracurium.[2]
Maximum concentration	10 mg/mL for IV push[7]; 0.2–0.5 mg/mL for continuous infusion.[2,24]
Preparation and delivery	Atracurium is an acidic solution; do not administer with alkaline solutions.[2,24] May be incompatible with propofol; however, the potential for incompatibility is concentration dependent and formulation specific.[24] For PN compatibility information, please see Appendix D.
IV push	10 mg/mL given rapidly or over 1 minute in patients with a history of histamine reactions.[2,24]
Intermittent infusion	No information available to support administration by this method. Bradycardia may be more common with atracurium than with other neuromuscular blocking agents.[2,3,7]
Continuous infusion	0.2–0.5 mg/mL.[2,24]
Other routes of administration	Should not be given IM due to tissue irritation.[2,7,24] No information available to support administration by other routes.

Atracurium Besylate

Comments

Significant adverse effects: Prolonged paralysis lasting 81 days was reported following atracurium infusion (20–75 mcg/kg/min) for 2 weeks in a 17-year-old patient.[23] The patient was also receiving corticosteroids, which may be a risk factor for this adverse effect. Prolonged paralysis has also been reported after following other neuromuscular blocking agents.[25–30] (See Drug Interactions below.)

Severe toxicity including death was reported in six neonates who received doses of 0.5 mg/kg. These babies ranged in gestational age from 24–37 weeks and in postnatal age from 1 day to 23 weeks. Toxicities included tachycardia, bradycardia, and oxygen desaturation. Three events resulted in death. The authors reported that atracurium could not be definitively linked to these outcomes but suggested lower doses (0.25 mg/kg) for neonates.[10]

Prolonged administration of atracurium may lead to the accumulation of its laudanosine metabolite. This metabolite has been associated with CNS irritation and seizures in animal models. Accumulation of laudanosine has been reported in patients with renal failure as well as those with hepatic failure, before and after liver transplantation, but generally at concentrations significantly lower than those associated with CNS excitation.[2,31–33]

Drug interactions: Enflurane and isoflurane anesthesia potentiate effects of atracurium; therefore, reduce atracurium dose by approximately 33% in these patients.[2,7,34] Also reduce atracurium dose in patients receiving succinylcholine or halothane.[2] Concomitant administration of atracurium with certain antibiotics (e.g., aminoglycosides, clindamycin, and vancomycin) may prolong neuromuscular blockade.[2,3,7] Consult appropriate resources for additional information on drug interactions.

Other: Neonates and infants generally require smaller doses than children; however, they recover more rapidly.[8] One report noted a 25% smaller dose.[11]

For neonatal nonemergent intubations, AAP recommends that vagolytic and muscle relaxant agents should be considered, and that analgesic agents or anesthetic doses of a hypnotic agent should be administered. Rocuronium or vecuronium is preferred over other available neuromuscular blocking agents.[35]

Atropine Sulfate

Brand names	AtroPen (auto-injector), generic
Medication error potential	None.
Contraindications and warnings	**Contraindications:** Patients with glaucoma, tachycardia, or any condition that inhibits postganglionic cholinergic nerves. Patients with asthma should not receive atropine as it can cause an excessive drying effect or mucous plugs in the bronchi.[1] In the event of life-threatening exposure to organophosphate insecticides or nerve agents, there are no absolute contraindications to treatment with atropine sulfate. However, caution should be observed when used in individuals with the diseases listed above.[2] **Warnings:** Caution in children with spastic paralysis or brain damage.[1] Children are at increased risk for increases in body temperature because of suppression of sweat. Children who receive larger doses are at risk for paradoxical hyperexcitability. Infants with Down syndrome may have increased sensitivity to cardiac effects and mydriasis. Use with caution in patients with hernia associated with esophageal reflux, hyperthyroidism, or cardiovascular disease. Psychosis may occur in some patients.[3]
Infusion-related cautions	Slow IV administration[3] or doses $<$0.1 mg[4] may cause paradoxical bradycardia.
Dosage	**Preanesthesia (to decrease secretions and block cardiac vagal reflexes during surgery)** **Infants:** 0.02–0.04 mg/kg 30–60 minutes preoperatively and then q 4–6 hr PRN.[3–7] **Children:** 0.01–0.02 mg/kg (0.1–0.4 mg) 30–60 minutes preoperatively and then q 4–6 hr PRN.[3,8,9] **Pulseless arrest** **Neonates:** Atropine is not included in the neonatal resuscitation guidelines.[10] **Infants and children:** 0.02 mg/kg (minimum 0.1 mg, maximum 0.5 mg) IV or IO; repeat if needed.[11] If given ET, use 0.04–0.06 mg/kg.[11] **Adolescents:** 0.02 mg/kg (minimum 0.1 mg, maximum 1 mg) IV or IO; repeat if needed.[11] **Physostigmine toxicity:** 0.5 mg for each 1 mg of the last dose of physostigmine administered.[12] **Organophosphate insecticide exposure in children:** 0.05 mg/kg (2–5 mg in *adults*) slowly (IV); may be doubled and repeated q 10–20 min until desired response (e.g., drying of excessive secretions).[13,14] **Hypertrophic pyloric stenosis**: Several have reported the successful use of IV atropine in doses that ranged from 0.005 to 0.02 mg/kg/dose IV given q 3–6 hr (before each feeding).[15–18]

Dosage *(cont.)*	**Nerve agent poisoning with cholinergic symptoms in children:** 0.05–0.1 mg/kg up to 4 mg repeated q 5–10 min until respiratory status improves or secretions resolve.[19,20] **AtroPen (auto-injector) for IM dosing. Should only be used for insecticide or nerve agent exposure and should only be administered by a trained individual.**[2] **<7 kg (generally <6 months of age):** 0.25 mg (yellow). **7–18 kg (generally 6 months to 4 years of age):** 0.5 mg (blue). **18–41 kg (generally 4–10 years of age):** 1 mg (dark red). **≥41 kg (generally >10 years of age):** 2 mg (green).
Dosage adjustment in organ dysfunction	None noted for use in preanesthesia, CPR, or physostigmine toxicity.[3,21] However, caution should be used in those with significant renal insufficiency who require multiple doses as in organophosphate insecticide exposure or nerve agent poisoning.[2]
Maximum dosage	**CPR/bradycardia:** 0.5 mg (child), 1 mg (adolescent).[3,11] **Nerve agent exposure:** 4 mg. Larger doses may be required in those with apnea, convulsions, cardiopulmonary arrest, or rapid progression of symptoms.[11,20] **Organophosphate poisonings:** Large doses may be required.[11,13] In one pediatric report, a patient received 86 doses, another patient received 61 doses (0.005–0.1 mg/kg/dose) in 24 hours, and another received 26 doses totaling 25 mg/kg over several days.[19]
Additives	Multiple-dose vials may contain methylparaben or benzyl alcohol.[22] (See Appendix C for specific information about potential adverse effects and toxicity.)
Suitable diluents	NS.[22] The AtroPen auto-injector should not be diluted.[2]
Maximum concentration	1 mg/mL (available commercially).[22] AtroPen doses are 0.25 mg, 0.5 mg, 1 mg, and 2 mg.[2]
Preparation and delivery	**Preparation:** Extemporaneously compounded atropine sulfate 2 mg/mL (diluted with NS) packaged in polypropylene syringes for use in the event of a terrorist nerve gas attack showed no visible changes and high-performance liquid chromatography (HPLC) analysis found no loss of the drug over 364 days at 5°C protected from light, 364 days at 23°C exposed to light, and 28 days at 35°C exposed to light.[22] **Storage:** Atropine sulfate injection should be stored at controlled room temperature. Freezing should be avoided. **Stability:** Atropine (salt form unspecified) 1 mg/mL repackaged in poly propylene syringes showed little or no change in concentration after 4 weeks of storage at room temperature.[22] Atropine sulfate 0.4 mg/mL repackaged in polypropylene and glass syringes were evaluated for physical and chemical stability over 4 days of storage at room temperature. There was no change in physical appearance, but HPLC analysis showed losses of 44% and 28% in the polypropylene and glass syringes, respectively, in 1 day. The losses were attributed to sorption to the rubber plunger tip since no decomposition peaks were observed. Analytical difficulties should be considered as a possible influence on these results, since these results are not consistent with other studies.[22]

Atropine Sulfate

IV push	Infuse rapidly.[2,3] If administered into a peripheral vein during CPR, follow dose with a normal saline flush to facilitate drug delivery to the circulation.[3]
Intermittent infusion	Not recommended.[3]
Continuous infusion	Continuous infusion was used in a 68-year-old *adult* with intentional ingestion of an organophosphate insecticide.[23]
Other routes of administration	May be given IM, SC (preoperatively), ET, or IO.[3,11] If injected in an extremity, the limb should be elevated for 10–20 seconds.[3] In preanesthesia induction, a faster onset of heart rate acceleration was reported following submental glossal injection than with deltoid or vastus lateralis injection.[24]
Comments	A 2-month-old given a 0.1-mg dose for bradycardia during ophthalmologic surgery subsequently had spontaneous extrusion of the lens and vitreous.[25] Children with accidental wartime exposures who were given atropine doses ranging from 0.01–0.17 mg/kg had few adverse events that included dilated pupils, tachycardia, dry mucous membranes, flushed skin, temperature >37.8°C, and neurologic abnormalities.[19] There were no fatalities or life-threatening dysrhythmias.

Azithromycin

Brand names	Zithromax
Medication error potential	Look-alike, sound-alike drug names. USP reports that azithromycin has been confused with azathioprine, aztreonam, erythromycin, and Zaroxolyn.[1] Zithromax has also been confused with Fosamax, Zoloft, Zyvox, Zinacef, Zovirax, and zinc sulfate.[1]
Contraindications and warnings	**Contraindications:** Should not be used in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide, or ketolide antibiotic.[2] **Warnings:** Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported.[2] If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. (See Infusion-Related Cautions section.) Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	Despite discontinuation of azithromycin and successful management of the allergic reaction, symptoms may recur after treatment is complete without further azithromycin exposure.[2] Patients required prolonged periods of observation and symptomatic treatment. Local IV site reactions have been reported.[2] The incidence and severity of these reactions were the same when 500 mg of azithromycin were given over 1 hour (2 mg/mL as 250-mL infusion) or over 3 hours (1 mg/mL as 500-mL infusion).[2]
Dosage	Very limited dosing information is available for IV use in pediatric patients. 10 mg/kg daily for 7 days, then 5 mg/kg daily for up to 5 weeks has been used in <72 hours old and <1000 g neonates for its anti-inflammatory effect. These patients were switched to oral therapy when tolerating full enteral feeds.[3] A single dose of 10 mg/kg has been given to pediatric patients aged 6 months to 16 years in a pharmacokinetics study.[4] **Community-acquired pneumonia (moderate to severe)** **Pediatric patients:** 10 mg/kg daily for 2 days has been given and then switched to oral dosing when possible.[5] **Adolescents:** 500 mg IV q 24 hr for a minimum of 2 days followed by 500 mg/day orally for a total of 7–10 days.[2,6–8] **Pelvic inflammatory disease:** 500 mg IV for 1–2 days, followed by 250 mg/day orally to complete 7 days of therapy.[2,9] If anaerobic organisms are suspected, an antimicrobial agent with anaerobic activity should be given concurrently.[2]
Dosage adjustment in organ dysfunction	Caution should be used in patients with impaired hepatic function.[2] Caution should also be exercised when administered in severe renal impairment (CrCl ≤10 mL/min).[2]
Maximum dosage	Little information is available, but generally 10 mg/kg/dose up to 500 mg.[2,4] Although serum concentrations have persisted for >10 days, a large IV dose (4 g) has been well-tolerated in healthy *adult* males.[10]

Azithromycin

Additives	None.
Suitable diluents	D5W, NS, ½NS, LR, D5LR, D5¼ NS, D5⅓NS, D5½NS, or D5½NS + 20 mEq KCl, Normosol-M in D5, and Normosol-R in D5.[2,11]
Maximum concentrations	2 mg/mL.[2,11] Patients receiving azithromycin at higher concentrations have experienced pain and local inflammation at the site during administration.[2,10]
Preparation and delivery	**Stability:** Stable for 24 hours at or below room temperature (30°C), or for 7 days under refrigeration (5°C).[2]
IV push	Not recommended.[2]
Intermittent infusion	1 mg/mL should be given over 3 hours.[2] Higher concentrations (2 mg/mL) and large doses (>500 mg) should be given over 1 hour.[2]
Continuous infusion	No information available.
Other routes of administration	Should not be given IM.[2,11]
Comments	**Rare adverse events:** One case of ototoxicity has occurred in an *adult* receiving IV azithromycin for 8 days.[12] Macrolide antibiotics may prolong cardiac repolarization and QT interval to cause cardiac arrhythmia and torsades de pointes.[2,13] A similar effect with azithromycin cannot be ruled out in patients at risk for prolonged cardiac repolarization.[2] Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported.[2] **Drug interactions:** Consult appropriate resources for dosing recommendations before combining any drug with azithromycin.

Aztreonam

Brand names

Azactam

Medication error potential

Look-alike, sound-alike drug names.

USP reports that aztreonam has been confused with azithromycin.[1]

Contraindications and warnings

Contraindications: In patients with known hypersensitivity to aztreonam or any other component in the formulation.[2]

Warnings: Although the manufacturer recommends caution when aztreonam is given to patients with immediate hypersensitivity reactions to penicillins or cephalosporins,[2] the cross-reactivity between cephalosporins and penicillins does not appear to extend to the monobactams. Patients with penicillin hypersensitivity have been given aztreonam without incident.[3–7] Similarly, those who experience hypersensitivity to aztreonam may not be hypersensitive to other beta-lactam antibiotics.[8] There is some suggestion that cross-sensitivity may occur between ceftazidime and aztreonam due to similar side chains.[4,5]

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2]

Infusion-related cautions

Although rare, anaphylactoid reactions may require immediate emergency treatment. Local reactions such as phlebitis, thrombophlebitis, discomfort, and swelling at the injection site have been reported.[2]

Dosage

Safety and effectiveness have not been established in those <9 months of age.[2]

Neonates

PNA	≤1200 g	1200–2000 g	≥2000 g
<7 days	60 mg/kg/day divided q 12 hr*[9]	60 mg/kg/day divided q 12 hr[9–11]	90 mg/kg/day divided q 8 hr[9–11]
≥7 days		90 mg/kg/day divided q 8 hr[9,12]	120 mg/kg/day divided q 6 hr[9,10]

*Until 4 weeks of age.

Infants and children

Mild-to-moderate infections: 90 mg/kg/day divided q 8 hr[2,9–12] up to 3 g/day.[9]

Severe infections: 90–120 mg/kg/day divided q 6 hr[2,9–12] up to 8 g/day.[9] 150 mg/kg/day have been used in febrile neutropenia.[13]

Cystic fibrosis *(P. aeruginosa)*: 200 mg/kg/day divided q 6 hr[10,11,14,15] up to 8 g/day.[9]

Dosage adjustment in organ dysfunction

If CrCl is 10–50 mL/min, give 50% of normal dose or 45–60 mg/kg/day divided q 8 hr; if CrCl is <10 mL/min, give 25% of normal dose or 15–20 mg/kg/day divided q 12 hr.[2,16] No adjustment in hepatic dysfunction.[2]

Maximum dosage

120 mg/kg/day[2] and 200 mg/kg/day (cystic fibrosis)[14,15] not to exceed 8 g/day.[2]

Additives

None.

Aztreonam

Suitable diluents	D5W, D10W, NS, LR, ¼NS, ½NS, D5¼NS, D5½NS, D5NS, and D5LR.[2] Use SW or BW, NS, or bacteriostatic NS for IM administration.[2,17]
Maximum concentration	≤20 mg/mL for IV infusion and 333 mg/mL for IM administration.[2,17]
Preparation and delivery	**Stability:** Following addition of diluent, contents should be shaken immediately and vigorously.[2] Solution may be colorless to light straw yellow and can develop a slight pink tint that does not affect potency.[2] **Compatibility:** See Appendix D for PN compatibility information.[18]
IV push	Over 3–5 minutes.[2,17]
Intermittent infusion	20–60 minutes.[2,17]
Continuous infusion	Has been reported in an adolescent at 260–350 mg/hr.[19]
Other routes of administration	May be given by deep injection into a large muscle in a concentration of <333 mg/mL.[11,12] (See Suitable Diluents section.) The dose should be given IV in patients with septicemia, localized parenchymal abscess, peritonitis, or when doses >1 g are administered.[12] Commercially-available frozen aztreonam injection in dextrose should only be used for IV infusion.[2] Aztreonam lysine is being investigated for inhalation administration in treatment of pseudomonal infections in cystic fibrosis patients. *The IV form should not be inhaled as it contains arginine, which can cause airway inflammation when used long-term.*[20,21]
Comments	**Laboratory interference:** May cause false elevations in SCr, liver enzymes, prothrombin, and thromboplastin times.[2] Positive direct Coombs tests have been reported.[2]

Baclofen

Brand names	Lioresal IT
Medication error potential	High-alert medication associated with significant patient harm should an error occur.[1] Look-alike, sound-alike drug names. Baclofen may be confused with bethanechol and Blocadren.[2] Lioresal may be confused with Lotensin.[2]
Contraindications and warnings	Not for IV, IM, SC, or epidural administration.[3] **U.S. boxed warning:** Abrupt withdrawal has caused severe sequelae including high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity.[3] In rare cases, rhabdomyolysis, multiple organ system failure, and death has occurred.[3] (See Comments section.) **Other warnings:** Should not be used for spasticity to maintain posture or balance.[3]
Infusion-related cautions	A sudden requirement for substantial dose escalation may indicate catheter complication (i.e., dislodgement).[3–6] Use extreme caution in filling implantable pump that allows direct access to the intrathecal (IT) catheter as direct injection through the catheter access port may cause a life-threatening overdose.[3]
Dosage	**IT administration (not intended for IV administration)** **Severe spasticity (spinal cord or cerebral origin)** Due to the nature of administration and need for pump implantation, usually a minimum patient weight of 15 kg is necessary.[7] **Test dose:** 50 mcg into IT space via barbotage over ≥1 minute.[3–6,8–15] Use 25 mcg in very small children.[3,14] If insufficient response within 4–8 hours, a second 75-mcg test dose can be given 24 hours after initial test dose.[3,8,10,12,14] If response continues to be inadequate, a third 100-mcg test dose[3,14,16] may be given 24 hours after the second test dose.[3,8] If an inadequate response continues, the patient is not a candidate for chronic IT baclofen therapy.[3] A significant decrease in muscle tone and/or frequency and/or severity of spasms is considered a positive response.[3] Patients with spasticity due to traumatic brain injury should not be evaluated for long-term IT baclofen until at least 1 year after the injury.[3] **Maintenance therapy:** Initial daily dose is based on the effective test dose and duration of its effects.[17] If the test dose response lasted ≤8 hours, the initial daily dose should be twice the test dose.[3,14] If the response lasted >8 hours, the initial daily dose should equal the test dose.[3,14] The dose should be increased every 24 hours by 5% to 15% until desired results are achieved.[3] The infusion rate (mcg/hr) is the total daily dose divided by 24 hours except when complex dosing is used.[3,18] (See Continuous Infusion section.) **≤12 years:** 100–300 mcg/day (4.2–12.5 mcg/hr).[3,18] Doses as large as 1000–1500 mcg/day have been used.[3,12,18] **>12 years:** 300–800 mcg/day (12.5–33.3 mcg/hr).[3,13,18] Doses as large as 2000 mcg/day have been used in *adults*.[18] If spasticity is of cerebral origin doses as large as 1000 mcg/day have been used.[3,10,17,18] Doses up to 1400 mcg/day have been given to children.[10,18]

Dosage *(cont.)*	**Neuroleptic malignant syndrome (NMS):** IT baclofen has been used successfully to treat NMS in *adults* and one pediatric patient.[23] **Tetanus:** IT baclofen has also been used successfully in treating muscle rigidity associated with tetanus in *adults*.[19–22]
Dosage adjustment in organ dysfunction	Patients with renal impairment may require smaller doses.[18]
Maximum dosage	Although doses up to 1500–2000 mcg/day have been given,[12,18] there is limited experience with dosages >1000 mcg/day.[3]
Additives	0.15 mEq sodium/mL.[3,24]
Suitable diluents	Sterile, preservative-free NS injection.[3,24]
Maximum concentration	50 mcg/mL (commercially available) for test dose. For maintenance dosing the commercially available strengths (i.e., 0.5 or 2 mg/mL) *must* be diluted if the patient requires strengths other than 0.5 mg/mL or 2 mg/mL.[3] IT refill kit concentration 0.5 mg/mL in 20-mL ampules or 2 mg/mL in 5-mL or 20-mL ampules.[3]
Preparation and delivery	**Delivery system issues:** Catheter complication may cause a sudden requirement for a substantial increase or decrease in dose.[3–6] Pump malfunction can also potentially lead to an overdose.[25] **Stability:** Because the product is preservative free, each vial is intended for single use only and any unused solution should be discarded. It does not require refrigeration and is stable at 37°C; however, storage temperature should not exceed 30°C, and it should not be frozen.[3,24] Appears to be stable in an implantable pump with morphine sulfate or clonidine without significant loss of either drug; however, <4% loss of morphine concentration occurred during a 30-day infusion course.[24]
IV push	Not intended for IV administration.[3]
Intermittent infusion	Not applicable.
Continuous infusion	Administered *intrathecally* via implantable pump device. Total daily dose in mcg divided by 24 hours = infusion rate.[3] Do not discontinue abruptly.[3] (See U.S. boxed warning in the Contraindications and Warnings section and see Comments section.) A complex (flex) dosing schedule has been described in the literature in both children and *adults* to allow for dosing *intrathecally* at varying rates to correspond with variation in muscle tone that occurs in a typical day (i.e., nighttime spasms in multiple sclerosis, etc.).[26,27]
Other routes of administration	Not intended for IM, IV, SC, or epidural administration.[3] *Intraventricular* administration has been reported as an alternative for patients with dystonia; may not be effective for spasticity.[28,29]

Baclofen

Comments

Significant adverse effects: Baclofen withdrawal syndrome can develop quickly into an emergent, life-threatening situation if not recognized and treated.[30] It can be difficult to diagnose because symptoms can be similar to sepsis,[31] meningitis, autonomic dysreflexia,[4,30] neuroleptic malignant syndrome,[32] and serotonin syndrome.[33] Patients can present with fever, tachycardia, seizures, and spasticity.[30–32,34,35] Even with early diagnosis and treatment patients can become refractory to therapy, and withdrawal can lead to morbidity and mortality[34,35] including rhabdomyolysis, elevated plasma creatine kinase, elevated liver function tests, organ failure, disseminated intravascular coagulation, and death.[30,32,34,36] This syndrome has been reported in *adults* and pediatric patients.[32,37,38]

A 10-year-old exhibiting dystonic-dyskinetic movements along with generalized tonic-clonic seizure activity (resembled status epilepticus) following a kink in the catheter essentially disrupting delivery of IT baclofen.[39]

A pump malfunction in a 12-year-old delivered a near-fatal dose of baclofen.[25] Reinitiate baclofen as soon as possible if withdrawal syndrome occurs.[3,30,34] Other treatment options include oral baclofen replacement,[3] benzodiazepines,[30,33,34,38] dantrolene sodium,[40] and cyproheptadine.[33,41] Withdrawal symptoms have persisted despite oral baclofen replacement therapy.[42]

Rare adverse effects: A study with *adult* patients found that IT baclofen increased seizures in patients with multiple sclerosis.[43,44] A pediatric study reported no change in the incidence/frequency of seizures in patients with spasticity of cerebral origin receiving IT baclofen.[10]

Monitoring: If a patient develops unexplained tolerance or symptoms of withdrawal despite continued infusion consider catheter leakage,[4,5,34] catheter dislodgement,[34] or pump failure.[6,34,45] One study recommends that cerebral spinal fluid (CSF) pressure should be measured prior to implantation to decrease risk of postoperative CSF leaks in patients with elevated CSF pressures.[46]

Complications: Infection of the implanted pump or catheter has been reported to occur in 4% to 12% of pediatric patients with spasticity.[47–49] Overall complications requiring surgery have been reported at a rate of 31% over a 3-year treatment period in pediatrics.[48] Children with dystonia experience a higher rate of complications than do those with spasticity.[50]

Bumetanide

Brand names	Bumex
Medication error potential	Look-alike, sound-alike drug names. USP reports that bumetanide has been confused with budesonide. Bumex has been confused with Demadex. No patient harm resulted.[1]
Contraindications and warnings	**Contraindications:** Patients with anuria.[2] (See Comments section.) **Warnings:** Patients with sulfonamide allergy may be hypersensitive to bumetanide.[2] Use cautiously in jaundiced neonates at risk for kernicterus. In vitro studies have shown bilirubin displacement in pooled cord blood samples from critically ill neonates.[2,3]
Infusion-related cautions	None noted.
Dosage	**Neonates** **Preterm neonates:** 0.01–0.05 mg/kg/dose q 24–48 hr.[4–6] 0.01–0.06 mg/kg/dose q 12–24 hr has been given to preterm (26 ± 2.75 weeks gestational age) neonates with oliguric acute renal failure.[7] A single dose of 0.05–0.1 mg/kg has been studied in neonates with respiratory failure.[6] **Term neonates:** 0.01–0.05 mg/kg/dose q 12–48 hr.[8] A larger dose has been studied in term neonates on extracorporeal membrane oxygenation (ECMO) therapy (0.1 mg/kg as a single dose).[9] Additionally, a single dose of 0.05–0.1 mg/kg has been studied in neonates with respiratory failure.[6] **Infants, children, adolescents:** 0.01–0.1 mg/kg/dose (up to 2 mg) BID, daily, or every other day.[10–13] A dose-ranging study found maximal diuretic responses in critically ill infants at doses of 0.035–0.04 mg/kg/dose and suggested a dosing interval of q 6–8 hr.[11] Usual dose in *adults* is 0.5–1 mg q 2–3 hr up to 10 mg/day.[2]
Dosage adjustment in organ dysfunction	Dosing adjustment is not required in renal dysfunction.[14] Larger doses (e.g., >2 mg in *adults*) may be required in patients with CrCl <5 mL/min.[15] May need to reduce dosage in patients with hepatic impairment.[4] During neonatal ECMO, the elimination half-life was longer[9] than that reported in preterm infants not on ECMO.[16] (See Comments section.)
Maximum dosage	0.1 mg/kg up to 10 mg/day has been used in *adults* with normal renal function.[15] Up to 20 mg/day have been given to *adults* with renal dysfunction.[15]
Additives	Benzyl alcohol.[2] (See Appendix C for specific information about potential benzyl alcohol toxicity.)
Suitable diluents	D5W, LR, or NS.[2,17]
Maximum concentration	0.25 mg/mL (available commercially).[2]

Bumetanide

Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information. **Photosensitivity:** Discolors when exposed to light.[17]
IV push	0.25 mg/mL over 1–2 minutes.[2,4,6,10–13]
Intermittent infusion	May be infused over a longer time than with IV push.[18]
Continuous infusion	In *adults* with chronic renal insufficiency, a loading dose of 1 mg followed by 0.912 mg/hr for 12 hours was more effective than two bolus doses of 6 mg given 6 hours apart.[18] Another study in *adults* reported onset of musculoskeletal symptoms within 8–48 hours of continuous infusions of doses ranging between 1 and 4 mg/hr.[19]
Other routes of administration	May be given IM.[2]
Comments	**Pharmacokinetics:** Half-life in preterm neonates with bronchopulmonary dysplasia was 5.8 ± 0.7 hours[16] and in 11 term neonates on ECMO was 13.2 ± 3.8 hours.[9] Infants 2.2 ± 1.6 months of age with lung disease had a half-life of 1.74 ± 1 hours, and those with heart disease had a half-life of 2.71 ± 1.59 hours.[12] **Adverse effects:** Electrolyte abnormalities, including hypokalemia, can occur; therefore, monitoring serum potassium concentration is important.[2] Ototoxicity may occur with large doses or prolonged IV therapy and may be additive when bumetanide is combined with aminoglycosides.[2]

Bupivacaine

Brand names	Marcaine, Sensorcaine, Sensorcaine-MPF
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that bupivacaine has been confused with levobupivacaine, lidocaine, and ropivacaine; no patient harm resulted.[2] USP reports that Marcaine has been confused with Sensorcaine; no patient harm resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** Convulsions followed by cardiac arrest with difficult resuscitation or death have occurred following the use of 0.75% bupivacaine for epidural anesthesia in obstetric patients; the 0.75% concentration of bupivacaine is not recommended for use in obstetrical anesthesia.[3] **Contraindications:** Bupivacaine is contraindicated in obstetrical paracervical block anesthesia (has resulted in fetal bradycardia and death).[3] Also contraindicated in patients with a hypersensitivity to bupivacaine or any amide anesthetic.[3] **Other warnings:** Bupivacaine should only be administered by persons specifically trained in the use of local anesthetics.[3] The FDA notified healthcare professionals in November 2009 of the risk of chondrolysis following continuous intra-articular infusion of local anesthetics, including bupivacaine, via elastomeric infusion devices. The FDA has received 35 reports of chondrolysis; some were in previously healthy young *adults,* and most following shoulder surgery. The cases had received the local anesthetics for postoperative pain for periods of 48–72 hours. Chondrolysis symptoms (joint pain, stiffness, loss of motion) occurred as early as 2 (median 5) months following therapy with the local anesthetic.[3,4]
Infusion-related cautions	*Not for IV infusion or IM administration. Administer only by infiltration, or by epidural, spinal, peripheral, or sympathetic nerve block as a single or repeat injections.*[5] Accidental IV injection may result in cardiac arrhythmia or cardiac arrest, seizures, coma, and respiratory arrest.[3] Oxygen, CPR, intubation equipment, medications, and trained personnel in emergency management should be immediately available when using bupivacaine.[3]
Dosage	Dose varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth and duration of anesthesia required, as well as individual response.[3] Once the catheter is placed, negative aspiration of blood or cerebrospinal fluid[6–11] with the absence of cardiovascular changes following a test dose indicates correct position of the catheter.[10,12,13] In neonates and infants, these tests alone may be insufficient; ultrasound guidance may aid in detecting proper catheter placement.[14,15] The manufacturer does not recommend the use of bupivacaine with or without epinephrine in children <12 years and the solution for spinal anesthesia should not be used in those <18 years.[3,6] However, epinephrine-containing solutions of bupivacaine have been used in neonates, infants, and children.[9,12,13] **Caudal block (preservative-free solution only)** **Infants and children:**1.25–2.5 mg/kg (0.5–1 mL/kg of the 0.25% solution).[6–11,17] To minimize potential for toxicity, some recommend using concentrations less than 0.25% in infants.[15]

Dosage *(cont.)*	**Peripheral nerve block:** 5 mL of 0.25% or 0.5% solution (12.5–25 mg).[18] **Sympathetic nerve block:** 20–50 mL of 0.25% solution (50–125 mg) (without epinephrine).[3,18] **Continuous epidural (caudal or lumbar) infusion (preservative-free solution only)** **Loading dose:** 1.25–2.5 mg/kg (0.5–1 mL/kg of 0.25% bupivacaine).[12,13,18,19] **Infusion:** Use with caution in infants due to reduced levels of alpha1-acid-glycoprotein leading to higher concentrations of unbound drug.[12, 13] **Neonates and infants ≤4 months:** 0.2–0.25 mg/kg/hr (0.08–0.1 mL/kg/hr of the 0.25% solution).[12,18,19] **Infants >4 months and children:** 0.375–0.5 mg/kg/hr (0.15–0.2 mL/kg/hr of the 0.25% solution).[13,18,19] **Continuous local infiltration for regional anesthesia:** 4 mL/hr of 0.5% solution (20 mg/hr) was continuously infused via a catheter placed adjacent to the operative site (NOT epidural or IT) for approximately 100 hours to provide analgesia in children >10 years old after posterior spinal fusion.[20]
Dosage adjustment in organ dysfunction	Reduce dosage and use with caution in patients with hepatic disease.[3,18] There is a potential for increased toxicity in patients with renal impairment, but no specific dosage adjustment is recommended.[3] Reduce dosage in patients with cardiac disease or in those who are acutely ill.[3,18]
Maximum dosage	In *adults*, do not exceed a maximum of 400 mg within a 24-hour period.[3,18]
Additives	Available with epinephrine 1:200,000. Products containing epinephrine should not be used for sympathetic nerve blocks.[3,18] Epinephrine-containing solutions contain metabisulfite.[3] (See Appendix C for more specific information about potential adverse effects of sulfites.) Multidose vials contain paraben preservatives and should not be used for epidural or caudal blocks.[3] (See Appendix C for more specific information about potential adverse effects of parabens.)
Suitable diluents	Not diluted.
Maximum concentration	0.75% (7.5 mg/mL) is available. However, the maximum recommended concentration varies by indication.[3,18] (See Dosage section.)
Preparation and delivery	Epinephrine containing solutions should not be used if they are a pinkish color, darker than slightly yellow, or if there is visible precipitate.[3,5]
IV push	Do not administer IV.[3,5,18] (See Infusion-Related Cautions section.)
Intermittent infusion	Do not administer IV.[3,5,18]
Continuous infusion	Do not administer IV.[3,5,18]

Bupivacaine

Other routes of administration	Do not administer IM.[3,5,18] One case report described IT bupivacaine 0.1–2 mg/kg/hr (with clonidine) in a 3-year-old child to provide palliative analgesia.[21]
Comments	**Significant adverse effects:** Systemic absorption of local anesthetics may result in toxic plasma concentrations, resulting in cardiovascular adverse effects, including decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, and cardiac arrest. Patients should be carefully monitored during injection. Use with caution in patients with underlying cardiovascular disease.[3,14,18,22] Fat emulsion 20%, in addition to standard resuscitative measures, has been used to treat severe cardiovascular toxicity due to systemic absorption or inadvertent systemic injection of bupivacaine. A neonate was treated with 1 mL/kg (0.2 g/kg),[14] and an adolescent was treated with 100 mL (2 mL/kg, 0.4 g/kg)[22] of 20% fat emulsion. Continuous infusions of bupivacaine in children has resulted in high plasma concentrations and seizures.[3] **Other:** Peripheral facial nerve paralysis lasting 8 hours has been reported after peritonsillar infiltration of bupivacaine in a 4-year-old child.[23] Products containing epinephrine may produce an exaggerated vasoconstrictor response resulting in ischemic injury or necrosis. Use with caution in areas with restricted or limited blood flow, such as the fingers.[3]

Caffeine Citrate

Brand names	Cafcit
Medication error potential	Use caution in calculation of dose and selection of formulation. The dose of caffeine base is 50% the dose of caffeine citrate. Do not interchange the caffeine citrate salt for the caffeine sodium benzoate salt formulation.
Contraindications and warnings	**Contraindications:** Documented hypersensitivity to caffeine or any of its components.[1] Do not interchange the caffeine citrate salt with the caffeine sodium benzoate formulation since the latter contains benzyl alcohol. The sodium benzoate product is contraindicated in neonates due to potentially fatal toxicities associated with gasping syndrome. (See Appendix C.) **Warnings:** Although no direct relationship has been established, necrotizing enterocolitis has been reported in newborns receiving caffeine.[1] (See Rare Adverse Effects in the Comments section.) Use cautiously in patients with a history of a peptic ulcer, impaired renal or hepatic function, seizure disorders, or cardiovascular disease. Avoid in those with symptomatic cardiac arrhythmias.[1]
Infusion-related cautions	None reported.
Dosage	Prior to initiation of caffeine citrate, baseline serum caffeine concentrations should be measured in infants previously treated with theophylline and in infants born to mothers who consumed caffeine prior to delivery.[1] The dose of caffeine base is 50% the dose of caffeine citrate (i.e., 20 mg of caffeine citrate is equivalent to 10 mg of caffeine base).[1] **Apnea of prematurity**[1–5] **Loading dose:** 10–40 mg/kg (as caffeine citrate) over 30 minutes. **Maintenance dose:** 5–8 mg/kg (as caffeine citrate) q 24 hr given over 10 minutes. Begin maintenance dose 24 hours after loading dose.[6,7] **Facilitate extubation in neonatal apnea** **Loading dose:** 20 mg/kg (as caffeine citrate) 24 hours prior to planned extubation. Should be given over 30 minutes. Doses as large as 80 mg/kg have been given.[6] **Maintenance dose:** 10–30 mg/kg, given over 10 minutes q 24 hr (as caffeine citrate). Begin maintenance dose 24 hours after loading dose.[6,7] In one report, neonates who received a loading dose of 80 mg/kg followed by 20 mg/kg/day resulted in a lower rate of extubation failure compared to those who received a loading dose of 20 mg/kg followed by 5 mg/kg/day.[6] **Treatment of postsedation paradoxical hyperactivity:** 63% of patients treated with 20 mg/kg (maximum of 200 mg) of caffeine citrate for postsedation paradoxical hyperactivity showed a positive effects and returned to baseline behavioral status after an average of 33 minutes ($p < 0.01$ compared to control group).[8]
Dosage adjustment in organ dysfunction	In neonates, approximately 86% of the drug is excreted unchanged in the urine, with the remainder metabolized by CYP1A2. Neonates with renal/hepatic dysfunction or those suffering from birth asphyxia should be monitored closely.[1] There are no recommendations for dosage adjustment in patients with renal impairment.[9]
Maximum dosage	Maximum loading dose of 80 mg/kg and maintenance dose of 30 mg/kg have been used.[6,7,10]

Caffeine Citrate

Additives	None.
Suitable diluents	D5W, D5W¼NS, D5W¼NS with 20 mEq KCl/L.[11]
Maximum concentration	20 mg/mL (as citrate) (commercially available).[1]
Preparation and delivery	**Stability:** Intact vials should be stored at room temperature.[11] There was <4% loss of caffeine citrate over a 60-day period when caffeine citrate (10 mg/mL) was stored at room temperature and under refrigeration at 4°C after repackaging in glass and plastic syringes (Becton-Dickinson).[11] Caffeine citrate is stable for 24 hours at room temperature when diluted to 10 mg/mL with D5W, D50W, Aminosyn 8.5%, dopamine 0.6 mg/mL, calcium gluconate 10%, heparin sodium 1 unit/mL, or fentanyl citrate 10 mcg/mL.[11] **Compatibility:** See Appendix D for PN compatibility information.[12]
IV push	Not recommended.
Intermittent infusion	Loading dose should be given over 30 minutes.[1,2,4] The maintenance dose is usually infused over 10–15 minutes[1,4]; however, it has been infused over 3 minutes.[5]
Continuous infusion	No reports.
Other routes of administration	None reported.
Comments	**Rare adverse events:** During a randomized, double-blind, placebo-controlled trial, six cases of necrotizing enterocolitis were identified among 85 neonates studied (caffeine = 46, placebo = 39). Caffeine citrate loading dose of 20 mg/kg followed by 5 mg/kg/day orally or intravenously, or placebo, was given to patients for up to 10 days. Four neonates receiving caffeine citrate and two receiving placebo developed necrotizing enterocolitis.[4] Caffeine is known to increase metabolic rate and oxygen consumption and may contribute to growth failure.[5] 2006 infants (500–1250 g) were randomly assigned to receive either caffeine or placebo for apnea of prematurity. Treatment was continued until it was no longer required. Caffeine improved the rate of survival without causing neurodevelopmental disability at 18–21 months in infants with very low birth weight.[10] **Monitoring:** Using standard dosage guidelines, a predicted concentration-time curve can be easily generated and routine monitoring of serum concentrations during treatment is probably not necessary unless a clinical problem arises.[2,13,14] If serum concentrations are monitored, the desired serum trough concentration ranges from 5–25 mg/L. Concentrations >50 mg/L are considered toxic.[1] **Drug interactions:** Caffeine is a substrate of CYP1A2.[1] It is an inhibitor of CYP1A2 and 3A4 (moderate). Consult appropriate resources for dosing recommendations before combining any drug with caffeine citrate.

Caffeine Citrate

Comments *(cont.)*

Pharmacokinetic considerations: Caffeine exhibits single-compartment, linear pharmacokinetics where both weight and age influence caffeine clearance.[2,3] In young infants, the elimination of caffeine is much slower than that in *adults* due to immature hepatic and/or renal function. In neonates, the half-life is approximately 3–4 days. By 9 months of age, the metabolism of caffeine approximates that seen in *adults*. Interconversion between caffeine and theophylline has been reported in preterm neonates (3% to 8% of caffeine would be expected to be converted to theophylline).[1]

Other: A multicenter, randomized controlled trial comparing infants who received 5 mg/kg/day versus 20 mg/kg/day of caffeine citrate showed no difference in adverse outcomes for development, temperment, and behavior at 1 year of age.[15]

Caffeine citrate has been shown to have acute hemodynamic effects (increased cardiac output and blood pressure) when given to hemodynamically stable patients with apnea of prematurity suggesting a potential role for caffeine in the treatment of hypotentive or hypoperfused infants.[16]

Calcitriol

Brand names

Calcijex

Medication error potential

Look-alike, sound-alike drug names.

USP reports that calcitriol has been confused with calcium carbonate, captopril, colestipol, paricalcitol, and ropinirole.[1]

Contraindications and warnings

Contraindications: Patients with hypercalcemia or evidence of vitamin D toxicity.[2] Vitamin D and its derivatives should be withheld during calcitriol therapy.[2]

Infusion-related cautions

None noted.

Dosage

Secondary hyperparathyroidism in hemodialysis patients: Initial dose based on parathyroid hormone (PTH) concentration.[2,3] Dose is given immediately after dialysis session. Both PTH and serum calcium concentration must be monitored closely. Serum Ca concentration should be ≤11 mg/dL and Ca × P product ≤75.

PTH Concentration	Dose
<500 pg/mL	0.5 mcg
500–1000 pg/mL	1.0 mcg
>1000 pg/mL	1.5 mcg

Dose can be increased by 0.25 mcg q 2 wk until ≤30% decrease in PTH. Calcitriol should be discontinued if hypercalcemia develops and the dose reduced when the drug is restarted.

Maintenance doses[3]

2–12 years: 0.04 mcg/kg (range = 0.5–2 mcg).

13–18 years: 0.02 mcg/kg (range = 0.25–2.25 mcg).

Prevention of calcitriol deficiency in acute lymphocytic leukemia patients: 0.25 mcg/day for children <30 kg and 0.5 mcg/day in those ≥30 kg.[4]

Hyperparathyroidism in peritoneal dialysis patients: In a 12-month study, 16 patients (12.5 ± 1.1 years) had an initial dose of 1 mcg added to 50–100 mL residual dialysate volume that was instilled into the peritoneal cavity after overnight exchanges 3 × week.[5] Dose was increased by 0.5 mcg if Ca <10.0 mg/dL and P <6 mg/dL. If Ca was >11 mg/dL, the dose was held until Ca was <11 mg/dL at which time calcitriol was restarted at 50% of the previous dose. Average maintenance dose was 1.3 ± 0.08 mcg.

Other uses

Hypocalcemia: An 8-month-old girl with hypocalcemic seizures and presumed rickets was given calcitriol 0.25 mcg 2 times a day (and calcium gluconate 4 times a day) for ≤2 days when she was changed to oral vitamin D and calcium.[6]

Of note: Hypocalcemic neonates ≤32 weeks gestational age (n = 19) failed to respond to large doses given IM.[7]

Dosage adjustment in organ dysfunction

None noted.

Calcitriol

Maximum dosage	0.06 mcg/kg has been given as single dose to adolescents.[8]
Additives	Contains polysorbate 20 and sodium ascorbate.[2,9] Some products contain edetate disodium dihydrate.[9]
Suitable diluents	D5W, NS, SW.[9]
Maximum concentration	2 mcg/mL (available commercially).[2,9]
Preparation and delivery	**Stability:** Up to 50% of calcitriol has been lost in 2 hours when calcitriol was placed in PVC; thus, use of PVC bags and sets is not recommended.[10]
IV push	Over 15 seconds.[8] May be given at the end of hemodialysis through venous catheter.[2]
Intermittent infusion	May be infused undiluted over 15 minutes.[11]
Continuous infusion	Not indicated.
Other routes of administration	1 or 2 mcg/mL has been added to a small volume of peritoneal dialysate and instilled intraperitoneally after nightly peritoneal dialysis.[5]
Comments	**Drug interactions:** Antacids containing magnesium should not be used during calcitriol treatment because of the potential for hypermagnesemia.[2] Hypercalcemia can cause cardiac arrhythmias in patients receiving digoxin; therefore, calcitriol should be used cautiously in these patients.[2] **Monitoring:** Hypercalcemia, hyperphosphatemia, and hypercalciuria can occur.[2,6] Monitor serum calcium and phosphorous concentrations once or twice a week during the first 12 weeks of treatment and during dose titration. If hypercalcemia occurs, discontinue therapy (including oral calcium phosphate binders) until serum calcium concentration normalizes.[2]

Calcium Chloride

Brand names	Various manufacturers
Medication error potential	Look-alike, sound-alike drug names. USP reports that calcium chloride has been confused with calcium gluconate. Patient harm resulted.[1]
Contraindications and warnings	**Contraindications:** Calcium chloride should not be used during CPR when ventricular fibrillation is present or in patients with the risk of existing digitalis toxicity.[2] Neonates receiving ceftriaxone should not be given calcium-containing fluids (e.g., Ringer's solution, Hartmann's solution, and PN formulations that contain calcium) because of the risk for precipitation of ceftriaxone–calcium salt.[3] Cases of fatal reactions with ceftriaxone–calcium precipitates in lungs and kidneys in neonates have been described.[3,4] In some cases the infusion lines and the times of administration of ceftriaxone and calcium-containing solutions differed.[3,4] Ceftriaxone and products that contain calcium may be administered sequentially to patients outside the neonatal period, as long as the infusion lines are thoroughly flushed between infusions with a compatible fluid.[3] Ceftriaxone should not be administered simultaneously with any calcium-containing solution via Y-site in any patient.[3] **Warnings:** Several different salt forms of calcium are available. Attention must be paid to the salt during product ordering, selection, and administration.[5]
Infusion-related cautions	Small veins (scalp, small hand, or foot) should not be used for infusion.[5] The infusion should be stopped if the patient complains of discomfort. Extravasation may cause tissue sloughing and necrosis.[6–9] (See Appendix E for management of extravasation.)
Dosage	10% (100 mg/mL) calcium chloride ($CaCl_2$) solution provides approximately 1.36 mEq/mL or 27.3 mg/mL of elemental calcium.[2,5] 1 mEq is equivalent to 20 mg elemental calcium. Dosing recommendations are expressed as mg or mg/kg of calcium chloride, or as mEq or mEq/kg of calcium. **Hypocalcemia in critically ill infants and children:** 10–20 mg/kg q 4–6 hr.[5,10] Ionized calcium measurements may be helpful in determining subsequent doses.[2] **Hypocalcemia secondary to infusion of blood products** **Neonatal exchange transfusion with citrated blood:** 0.45 mEq (0.33 mL of 10% $CaCl_2$) after each 100 mL blood exchanged.[11] **Citrated blood transfusion in *adults*:** 1.35 mEq (1 mL of 10% $CaCl_2$) per 100 mL blood transfused, administered concurrently with transfusion.[11] $CaCl_2$ infusion (5 mg/kg) during fresh frozen plasma administration decreased citrate-induced hypocalcemia in children with thermal injury.[12] **Cardiac arrest with documented hypocalcemia, hypermagnesemia, hyperkalemia, or calcium channel blocker overdose:** (Routine administration during CPR is no longer recommended. Infusion through a central line is preferred.)[13] **Pediatric patients:** 20 mg/kg (0.2 mL/kg of 10% $CaCl_2$; 0.272 mEq/kg) not to exceed 2000 mg/dose.[2,5,13,14] If beneficial, a continuous infusion of 20–50 mg/kg/hr may be infused. Titrate infusion according to hemodynamic parameters; avoid hypercalcemia.[5,13]

Calcium Chloride

Dosage *(cont.)*	***Adults*:** ACLS Guidelines recommend against routine administration during CPR and suggest consideration of calcium administration for *adults* with cardiac arrest in the following scenarios[15]: **Hyperkalemia or hypermagnesemia:** 500–1000 mg infused over 2–5 minutes.[15] **Beta-blocker overdose or shock refractory to other measures:** 20 mg/kg over 5–10 minutes followed by a continuous infusion of 20 mg/kg/hr. Titrate infusion according to hemodynamic parameters; avoid severe hypercalcemia (ionized calcium greater than twice the upper limit or normal).[15]
Dosage adjustment in organ dysfunction	Urinary excretion accounts for 20% of calcium elimination.[2] Calcium concentrations should be monitored closely in patients with renal dysfunction who require calcium.[5]
Maximum dosage	1000 mg/dose in *adults*.[2,5] 2000 mg/dose for children and adolescents in cardiac arrest.[13]
Additives	Aluminum is present as a contaminant in amounts up to 1000 mcg/L.[2]
Suitable diluents	Most standard dextrose- and/or saline-containing IV fluids.[16]
Maximum concentration	Undiluted, 100 mg/mL.[2]
Preparation and delivery	**Compatibility:** Often incompatible with bicarbonate, sulfate- or phosphate-containing fluids; consult a detailed reference and consider other additives' impact on solubility.[5,16] Calcium-containing fluids should not be co-infused with ceftriaxone.[3] Calcium-containing fluids should not be co-infused with PN because of the risk for precipitation with the phosphate component. If no other IV access is available and the two must be co-infused, consult a detailed compatibility reference that considers the parenteral protein formulation and concentrations of PN additives.[16]
IV push	Slow, over 3–5 minutes; not to exceed 100 mg/min.[2]
Intermittent infusion	Dilute to a final concentration of 20 mg/mL and infuse over an hour.[5]
Continuous infusion	20 mg/mL concentration at 20–50 mg/kg/hr.[5,13]
Other routes of administration	IM or SC administration should not be used.[2] IO administration may be used during CPR.[13]
Comments	**Drug interactions:** IV calcium should be used cautiously in patients receiving cardiac glycosides because of the potential for development of arrhythmias.[2]

Calcium Gluconate

Brand names	Various manufacturers
Medication error potential	Look-alike, sound-alike drug names. USP reports calcium gluconate has been confused with calcium carbonate; no harm resulted.[1] USP also reports that calcium gluconate has been confused with calcium chloride, which did result in patient harm.[1]
Contraindications and warnings	**Contraindications:** Calcium chloride should not be used during CPR when ventricular fibrillation or hypercalcemia is present, or in patients with the risk of existing digitalis toxicity.[2] Neonates receiving ceftriaxone should not be given calcium-containing fluids (e.g., Ringer's solution, Hartmann's solution, and PN formulations that contain calcium) because of the risk for precipitation of ceftriaxone–calcium salt.[3] Cases of fatal reactions with ceftriaxone–calcium precipitates in lungs and kidneys in neonates have been described.[3,4] In some cases the infusion lines and the times of administration of ceftriaxone and calcium-containing solutions differed.[3,4] Ceftriaxone and products that contain calcium may be administered sequentially to patients outside the neonatal period, as long as the infusion lines are thoroughly flushed between infusions with a compatible fluid.[3] Ceftriaxone should not be administered simultaneously with any calcium-containing solution via Y-site in any patient.[3] **Warnings:** Several different salt forms of calcium are available. Attention must be paid to the salt during product ordering, selection, and administration.[5]
Infusion-related cautions	Small veins (scalp, small hand, or foot) should not be used for infusion.[2] The infusion should be stopped if the patient complains of discomfort. Extravasation may cause tissue sloughing and necrosis[6–10] (See Appendix E for management of extravasation.) Infusion through an umbilical artery catheter in neonates was associated with superficial and deep skin necrosis in five infants and with necrotizing enterocolitis in one infant.[11] Intra-arterial infusion may cause vasospasm.[12] Rapid injection may cause vasodilation, hypotension, bradycardia, arrhythmias, syncope, and cardiac arrest.[2]
Dosage	10% (100 mg/mL) calcium gluconate solution provides approximately 0.465 mEq/mL or 9.3 mg/mL of elemental calcium.[2] 1 mEq is equivalent to 20 mg elemental calcium. Dosing recommendations are expressed as mg or mg/kg of calcium gluconate, or as mEq or mEq/kg of calcium. **Daily maintenance calcium IV**[5] **Neonates:** 3–4 mEq/kg/day. **Infants and children <25 kg:** 1–2 mEq/kg/day. **Children 25–45 kg:** 0.5–1.5 mEq/kg/day. **Children >45 kg, adolescents and *adults*:** 0.2–0.3 mEq/kg/day or 10–20 mEq/day. **Hypocalcemia (dosing should be guided by monitoring serum calcium concentrations)** **Neonates:** 200 mg/kg[5,13,14] to 400 mg/kg/day as a continuous infusion or divided q 6–8 hr.[12,15–18] Doses as large as 800 mg/kg/day have been used.[12] **Infants and children:** 200–500 mg/kg/day as a continuous infusion or divided q 6 hr.[5] **Adolescents and *adults*:** 2–15 g/day as a continuous infusion or divided q 6 hr.[5]

Dosage *(cont.)*

Hypocalcemia secondary to infusion of blood products: 0.45 mEq (approximately 1 mL of 10% calcium gluconate) per 100 mL of citrated blood.[5]

Tetany

Neonates, infants, and children: 500 mg/kg/day divided q 6 hr or as a continuous infusion.[5,19] Intermittent doses should be infused over 5–10 minutes.[5]

***Adults*:** 1–3 g/dose infused over 10–30 minutes. May repeat after 6 hours.[5]

Hyperkalemia: One study reported safe and effective use of a compounded multicomponent solution containing 3000 mg calcium gluconate, 150 g dextrose, 30 units regular insulin, and 100 mEq sodium acetate (final volume approximately 556 mL) infused at 2 mL/kg/hr for 1 hour followed by 1 mL/kg/hr to treat hyperkalemia in 21 patients. The solution resulted in a calcium gluconate infusion of 10.8 mg/kg/hr for 1 hour then 5.4 mg/kg/hr until resolution of hyperkalemia.[20]

Cardiac arrest with documented hypocalcemia, hypermagnesemia, hyperkalemia, or calcium channel blocker overdose: (Routine administration during CPR is no longer recommended. Calcium chloride is preferred over calcium gluconate in critically ill children; however, in nonarrest scenarios with only peripheral venous access, calcium gluconate is preferred.)[21,22]

Pediatric patients: 60–100 mg/kg/dose (max 3000 mg/dose) infused over 2–5 minutes.[5,22]

***Adults*:** ACLS Guidelines recommend against routine administration during CPR and suggest consideration of calcium administration for *adults* with cardiac arrest in the following scenarios[23]:

Hyperkalemia or hypermagnesemia: 1500–3000 mg infused over 2–5 minutes.[23]

Beta-blocker overdose or shock refractory to other measures: 60 mg/kg over 2–5 minutes followed by a continuous infusion of 60 mg/kg/hr. Titrate infusion according to hemodynamic parameters; avoid severe hypercalcemia (ionized calcium greater than twice the upper limit of normal).[23]

Dosage adjustment in organ dysfunction

Calcium concentrations should be monitored closely in patients with renal dysfunction who require calcium.[5]

Maximum dosage

For neonates, 800 mg/kg/day as a continuous infusion or in 4 divided doses.[5,12] For older infants and children, 500 mg/kg/day as continuous infusion or in 4 divided doses.[5]

Additives

Aluminum is present as a contaminant.[2] Polyethylene vials contain significantly less contaminant aluminum than calcium gluconate in glass vials.[24]

Suitable diluents

D5LR, D5NS, D5W, D10W, D20W, LR, NS.[25]

Maximum concentration

Undiluted, 100 mg/mL.[2]

Preparation and delivery

Compatibility: Often incompatible with bicarbonate, sulfate- or phosphate-containing fluids; consult a detailed reference and consider other additives' impact on solubility.[5,25] Calcium-containing fluids should not be co-infused with ceftriaxone.[3]

Calcium-containing fluids should not be co-infused with PN because of the risk for precipitation with the phosphate component. If no other IV access is available and the two must be co-infused, consult a detailed compatibility reference that considers the parenteral protein formulation and concentrations of PN additives.[25]

Calcium Gluconate

IV push	Slow, over 2–5 minutes.[5,22] In *adults*, 200 mg (2 mL of 10% calcium gluconate solution) over 1 minute.[2]
Intermittent infusion	Dilute to final concentration of 50 mg/mL and infuse over 10 minutes to 1 hour.[5]
Continuous infusion	50 mg/mL.[5]
Other routes of administration	IM or SC administration should not be used.[2,5]
Comments	**Drug interactions:** IV calcium should be used cautiously in patients receiving cardiac glycosides because of the potential for development of arrhythmias.[2] **Adverse effects:** Bradycardia, hypotension, and cardiac arrhythmias may occur.[2] Calcinosis cutis occurred in an 11-year-old boy within 3 weeks of calcium gluconate infusion.[26] Extravasation of calcium gluconate in a premature neonate resulted in calcinosis cutis and compartment syndrome.[27] **Other:** Calcium gluconate bioavailability is considered to be less than that of calcium chloride. In 49 critically ill children aged 1 day to 17 years who received equivalent doses of either calcium chloride or calcium gluconate (0.136 mEq/kg) for hypocalcemia, ionized calcium concentrations were increased 30 minutes after the infusion in both groups; however, patients who received calcium chloride had greater increases in ionized calcium compared to those who received calcium gluconate.[28] In 10 stable burn patients aged 13 months to 17 years who received equivalent infusions of calcium chloride and calcium gluconate (0.035 mEq/kg) in a crossover study, ionized calcium concentrations were not different 10 minutes after infusion.[29]

Caspofungin

Brand names	Cancidas
Medication error potential	None reported by ISMP or USP.[1,2]
Contraindications and warnings	**Contraindications:** Documented hypersensitivity to caspofungin or any of its components.[3] **Warnings:** Transient elevations in alanine transaminase (ALT) and aspartate aminotransaminase (AST), as well as, isolated cases of clinically significant hepatic dysfunction, hepatitis, and hepatic failure have been reported.[3,4] Cases of hepatobiliary adverse events have been noted in postmarketing surveillance.[5] (See Drug Interactions in the Comments section.) Caspofungin should be limited to patients for whom the potential benefit outweighs the potential risk.[3]
Infusion-related cautions	Possible histamine-mediated symptoms (flushing, urticaria, pruritus and bronchospasm), including anaphylaxis, have been reported.[3]
Dosage	**Neonates (preterm and term) and infants <3 months of age:** Initial (i.e., loading) doses of 1.5–8 mg/kg/day on day 1 followed by 1–6 mg/kg/day have been reported.[6–8] A 6-week-old (24 weeks gestational age) neonate received a loading dose of 50 mg/m^2/day followed by a maintenance dose of 35 mg/m^2/day.[9] Other reports have given 1 mg/kg/day for 2 days followed by 2 mg/kg/day[10–12] and 5 mg/kg/day (50 mg/m^2) for 3 days followed by 2.5 mg/kg/day (25 mg/m^2).[13] **Neonates, infants, children (≥3 months up to 17 years of age):** It is recommended to use body surface area (BSA) (see Appendix A) for caspofungin dosing (see Pharmacokinetic Considerations in the Comments section). Loading dose of 70 mg/m^2/day on day 1, followed by 50 mg/m^2/day thereafter (maximum loading dose and maintenance dose should not exceed 70 mg).[3,12,14–20] ***Adults*:** 70 mg/day for 1 day followed by 50 mg/day.[3,12,14,21]
Dosage adjustment in organ dysfunction	No dosage adjustment is recommended with renal impairment or mild hepatic impairment. With moderate to severe hepatic impairment (Child Pugh score of >7–9), dose adjustment is recommended.[3,22]
Maximum dosage	70 mg/day.[3,14–16] 100 mg/day has been given to *adults* and a 13-year-old.[3,23]
Additives	May contain parabens or 0.9% benzyl alcohol if BW is used for reconstitution.[3] (See Appendix C for more specific information about potential adverse effects of parabens and about potential adverse effects and/or benzyl alcohol toxicity in neonates.)
Suitable diluents	SW, NS, BW (for reconstitution); NS, ½NS, ¼NS, LR for further dilution.[3,24] Do not use dextrose-containing solutions as diluents.[3,24]
Maximum concentration	0.5 mg/mL.[3]

Caspofungin

Preparation and delivery	Not recommended to admix or infuse concomitantly with other drugs, but evidence exists supporting Y-site administration for a number of different medications.[3,24] Check IV compatibility listings.
IV push	Not recommended.
Intermittent infusion	Administer (0.1–0.5 mg/mL) over 1 hour.[3,24]
Continuous infusion	Not reported.
Other routes of administration	Not reported.

Comments

Drug interactions: Caspofungin is a weak substrate for CYP450.[25] Drug interactions are possible when used with tacrolimus and cyclosporine and certain inducers or inhibitors of CYP450.[3] Concomitant use of inducers (rifampin, efavirenz, nevirapine, phenytoin, dexamethasone and carbamazepine) may decrease caspofungin concentrations; thus, caspofungin doses may need to be increased up to 70 mg/m^2/day (maximum: 70 mg/day).[3] Consult appropriate resources for dosing recommendations before combining any drug with caspofungin.

Cyclosporine increases the AUC of caspofungin by approximately 35%.[3] Concomitant cyclosporine use has also been associated with increases in ALT (2–3 times the upper limit of normal) and AST.[3]

Pharmacokinetic considerations: Caspofungin exhibits log-linear pharmacokinetics where both weight and age influence clearance. The beta (distribution) phase half-life is 30% to 40% lower in pediatric patients than in *adult* patients. The shorter caspofungin beta-phase half-life observed in children relative to that in *adults* is most likely due to an increase in the relative rate of plasma clearance as suggested by both the weight-normalized and BSA-normalized clearance. Caspofungin uptake into tissue cells is increased in children relative to *adults*, with highest concentrations seen in the liver. Minimal metabolism and excretion occur during the first 30 hours postdose.[3,15,16]

Pharmacokinetic studies have found that BSA-based dosing regimens, compared to mg/kg/day-based dosing regimens produce similar concentrations to those seen in *adults*.[15,16,25] 1 mg/kg/day resulted in suboptimal concentrations in a pharmacokinetic study of children and adolescents.[16]

Other: 2 mg/kg/day for 1 day followed by 1.5 mg/kg/day has been used successfully in combination with liposomal amphotericin B in a 24-month-old.[26]

CeFAZolin Sodium

Brand names	Generic
Medication error potential	ISMP recommends tall man lettering to decrease confusion between ceFAZolin and cefTRIAXone.[1] USP reports that ceFAZolin may be confused with ampicillin, cefepime, cefotaxime, cefoxitin, Cefotan, cefotetan, ceftriaxone, cefprozil, ceftazidime, ceftizoxime, cefuroxime, cephalexin, oxacillin, Rocephin, and Zosyn.[2]
Contraindications and warnings	**Contraindications:** Do not use in patients with immediate-type hypersensitivity reactions to cephalosporins.[3] **Warnings:** Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins.[3] (See Appendix C for specific information.) Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[3] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.[3]
Infusion-related cautions	If given to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. (See Appendix C.)
Dosage	**Neonates:** Safety in patients <1 month has not been established.[3] However, 40 mg/kg/day divided q 12 hr has been used in premature neonates ≤2000 g until 4 weeks of age.[4] **Infants and children** **Mild-to-moderate infections:** 25–100 mg/kg/day divided q 6–8 hr.[3,5–7] **Severe infections:** 50–100 mg/kg/day divided q 6–8 hr.[3,7,8] **Bacterial endocarditis** **Prevention (for dental procedure*):** 50 mg/kg not to exceed 1 g given 30–60 minutes prior to a procedure.[7,9] Only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome. (See Comments section.) **Procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.*[9] **Treatment (oxacillin-susceptible staphylococci in nonanaphylactoid penicillin-allergic patient)** **Absence of prosthetic material:** 100 mg/kg/day divided q 8 hr with or without gentamicin for 3–5 days.[10] **Prosthetic valve endocarditis:** 100 mg/kg/day divided q 8 hr plus rifampin for ≥6 weeks; plus gentamicin for 2 weeks.[10] **Perioperative prophylaxis:** Dose of 25 mg/kg administered 30 minutes to 1 hour prior to the start of surgery.[7] May need to redose during surgery for lengthy operative procedures longer than 2 hours.[3]
Dosage adjustment in organ dysfunction	If CrCl is 40–70 mL/min, give 60% of the normal daily dose divided q 12 hr.[3] If CrCl is 20–40 mL/min, give 25% of the normal daily dose divided q 12 hr.[3] If CrCl is 5–20 mL/min, give 10% of the normal daily dose q 24 hr.[3] Another reference recommends giving 50 mg/kg/day divided q 12 hr if CrCl is 10–29 mL/min, and 25 mg/kg q 24 hr if CrCl is <10 mL/min.[11]

CeFAZolin Sodium

Maximum dosage	100 mg/kg/day,[3,10] not to exceed 6 g/day in children and 12 g/day in *adults*.[3]
Additives	2.1 mEq (48 mg) sodium/g of ceFAZolin.[3]
Suitable diluents	D5LR, D5NS, D5½NS, D5¼NS, D5W, D10W, LR, NS, SW, or R.[3,12]
Maximum concentration	77 mg/mL (in D5W), 69 mg/mL (in NS), and 138 mg/mL in SW.[13] Concentrations of 225–330 mg/mL have been used for IM administration.[3]
Preparation and delivery	**Stability:** No change in potency when color is pale yellow to yellow.[3,12] Store intact vials at room temperature and protect from light.[3,12] Reconstituted solution is stable for 24 hours at room temperature or 10 days when refrigerated[12]; thawed solutions of the commercially available, frozen ceFAZolin injections are stable for 48 hours at room temperature or 30 days when refrigerated.[3] Shake well before use.[3] **Compatibility:** See Appendix D for PN compatibility information.[14]
IV push	Over 3–5 minutes.[12] In fluid-restricted patients, 138 mg/mL has been administered.[13]
Intermittent infusion	5–20 mg/mL[3,12]
Continuous infusion	Although no specific information is available, other beta-lactam antibiotics have been given by this method.[15] Manufacturer states that ceFAZolin may be administered by continuous infusion.[3]
Other routes of administration	Reconstitute in SW (225–330 mg/mL) and give by deep IM administration.[12]
Comments	**Rare adverse events:** Cephalosporin-induced hepatitis can present as cholestatic hepatitis and eosinophilic hepatitis.[3] Cephalosporins may inhibit vitamin K dependent clotting factors.[16] **Laboratory interference:** False–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used. Glucose oxidase methods (Diastix, TEST-TAPE, Clinistix) are not associated with false–positive test results.[3] May also cause false increase serum or urine creatinine.[3] Positive direct and indirect Coombs tests have been reported and may also occur in newborn infants whose mothers received cephalosporins before delivery.[3] **Drug interactions:** Probenecid may decrease renal tubular secretion and increase serum concentrations of ceFAZolin.[3] **Other:** Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable: (1) prosthetic cardiac valve or prosthetic material used for cardiac valve repair; (2) previous infective endocarditis; (3) congenital heart disease (CHD) in a person with a) unrepaired cyanotic CHD including palliative shunts and conduits, b) completely repaired congenital heart defect with prosthetic material or device whether placed by surgery or by catheter intervention during the first 6 months after the procedure, and c) repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization); and (4) cardiac transplantation recipients who develop cardiac valvulopathy.[9]

Cefepime

Brand names	Maxipime
Medication error potential	Look-alike, sound-alike drug names. USP reports that cefepime has been confused with cefazolin, cefixime, cefotaxime, cefotetan, Cefotan, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, and ceftizoxime.[1] USP also reports confusion for Maxipime with cefotaxime and ceftazidime and Maxaquin.[1]
Contraindications and warnings	**Contraindications:** Should not be used in those with a known allergy to cefepime or another cephalosporin antibiotic, penicillin, and other beta-lactam antibiotics.[2] **Warnings:** Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins (10%).[2] (See Appendix C for specific information.) Adjust dosage in those with renal dysfunction (CrCl ≤60 mL/min).[2] Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.[2] Pain or phlebitis may occur at the injection site.[2]
Dosage	**Neonates** **≤14 days (term and preterm):** 60 mg/kg/day divided q 12 hr.[3] **>14 days or pseudomonas infection:** 100 mg/kg/day divided q 12 hr.[3,4] **Infants and children (2 month–16 years)** **Mild-to-moderate infection:** 100–150 mg/kg/day divided q 8 hr[5] or 12 hr.[2,6] **Severe infections:** 150 mg/kg/day divided q 8 hr.[2,5] **Adolescents or patients >40 kg:** 1–4 g/day divided q 12 hr.[2] **Bacterial endocarditis (treatment of culture negative within 1 year of prosthetic valve infection):** 150 mg/kg/day divided q 8 hr for 6 weeks (plus gentamicin, vancomycin, and rifampin).[7] **Cystic fibrosis (acute pulmonary exacerbation):** 150 mg/kg/day (up to 2 g/dose) divided q 8 hr.[8,9] **Febrile neutropenia** **Infants and children (2 months–16 years):** 150 mg/kg/day divided q 8 hr.[3,10–13] **Adolescents or those >40 kg:** 6 g/day divided q 8 hr.[2,6]

Dosage *(cont.)*	**Meningitis:** Although cefepime has been given to treat meningitis (150 mg/kg/day divided q 8 hr),[7,8] the manufacturer recommends that patients with suspected or documented meningitis should receive an alternate antibiotic with demonstrated clinical efficacy.[2] **Skin and soft tissue infections, urinary tract infections (including pyelonephritis), pneumonia, and lower respiratory tract infections:** Infants and children should receive 150 mg/kg/day divided q 8–12 hr.[3,9–13]
Dosage adjustment in organ dysfunction	If CrCl is >50 mL/min, give normal dose q 8–12 hr; if 10–50 mL/min, give q 24 hr; and if <10 mL/min, give q 48 hr.[14] The manufacturer recommends dose adjustment when CrCl ≤60 mL/min.[2] If not adjusted, serious adverse reactions, including life-threatening or fatal occurrences of encephalopathy, myoclonus, and seizures may occur.[2] No adjustment in impaired hepatic function.[2] Unlike other cephalosporins, no dosage adjustment is needed for burn patients.[15]
Maximum dosage	2 g/dose.[2]
Additives	None.
Suitable diluents	D5W, D10W, NS, D5NS, D5LR, Normosol-M in D5, or Normosol–R in D5, sodium lactate ⅙M.[2,16]
Maximum concentration	280 mg/mL for IM[2,16] and 160 mg/mL for IV administration.[2,16]
Preparation and delivery	**Stability:** Before reconstitution store at 2°C to 25°C.[2] Reconstituted vials are stable for 7 days if refrigerated (5°C) or for 24 hours at room temperature (25°C).[2,16] Do not refreeze.[2] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Although not generally administered by this method, doses of 2 g have been given over 3–5 minutes in *adults*.[17]
Intermittent infusion	10–40 mg/mL over 30 minutes.[2,16]
Continuous infusion	3–4 g/day over 24 hours (125–167 mg/hr) at a concentration of 3–4 mg/mL in *adults*.[18] Prolonged infusions over 3–4 hours have been used in *adults*[19] and over 3 hours in children.[20]
Other routes of administration	IM administration.[2,16] Diluted in D5W, 0.5 or 1% lidocaine, BW, SW, or NS to a maximum concentration of 280 mg/mL.[2,16]

Cefepime

Comments

Rare adverse events: Aminoglycosides may increase the potential of nephrotoxicity and ototoxicity.[2] Likewise, potent diuretics (e.g., furosemide) have been associated with nephrotoxicity.[2]

Many cephalosporins can cause a decrease in prothrombin activity.[2] The drug may also suppress the gut flora that normally synthesizes these clotting factors. Patients with renal or hepatobiliary impairment or poor nutritional status, and those with cancer have an increased risk for this adverse effect.[2] Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated. (See Appendix C for specific information.)

Cefepime may induce seizure activity in patients with normal renal function.[21]

Monitor: CBC, prothrombin time (especially if on warfarin); signs and symptoms of *Clostridium difficile*–associated diarrhea.

Drug interactions: Cephalosporins may enhance the anticoagulant effect of vitamin K antagonists (e.g., warfarin). Concomitant use of probenecid may increase the AUC of cefuroxime.[2] Consult appropriate resources for dosing recommendations before combining any drug with cefepime.

Laboratory interference: False–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used. It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used. Positive direct Coombs tests have been reported during treatment with cefepime.[2]

Cefotaxime Sodium

Brand names

Claforan

Medication error potential

USP reports that cefotaxime sodium has been confused with cefazolin, cefepime, Cefotan, cefotetan, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, cefuroxime and Maxipime. Claforan has been confused with Cefotan and Cleocin.[1]

Contraindications and warnings

Contraindications: Should not be used in those with a known allergy to cefotaxime or another cephalosporin antibiotic.[2]

Warnings: Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins. Cefotaxime should be given cautiously to these patients.[2] (See Appendix C for specific information.)

A potentially life-threatening arrhythmia has been reported in six patients who received cefotaxime by rapid bolus injection (<60 seconds) through a central venous catheter.[2]

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]

Infusion-related cautions

If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.[2]

Dosage

Neonates: The manufacturer indicates that it is not necessary to differentiate between premature and normal gestational age infants[2]; however, others have recommended the following dosing regimens:

PNA	≤1200 g	1200–2000 g	≥2000 g
<7 days	100 mg/kg/day divided q 12 hr[2–5]*	100 mg/kg/day divided q 12 hr[2–5]	100–150 mg/kg/day divided q 8–12 hr[2,4,5]
≥7 days		150 mg/kg/day divided q 8 hr[2–5]	150–200 mg/kg/day divided q 6–8 hr[2,4,5]

*Until 4 weeks of age.

Doses as small as 50 mg/kg/day given as a single dose or divided q 12 hr may provide effective serum concentrations for non-CNS infections in very low birth weight infants.[6,7]

Infants and children

Mild-to-moderate infections: 75–100 mg/kg/day (up to 4–6 g/day) divided q 6–8 hr.[4]

Severe infections: 150–300 mg/kg/day (up to 8–10 g/day) divided q 6–8 hr.[4,8]

The manufacturer recommends 50–180 mg/kg/day divided q 4–6 hr if <50 kg.[2]

Adolescents and *adults*: Usual dose 2 g/day given as a single dose or divided q 12 hr.[2] Depending on severity of infection, may be treated with 2 g/dose q 6, 8, or 12 hr up to 12 g/day.[2]

Meningitis: For neonates see maximum doses in above table. 200–300 mg/kg/day divided q 6–8 hr.[4,9–12]

Dosage adjustment in organ dysfunction

If CrCl is 30–50 mL/min, give normal dose q 8–12 hr; if 10–29 mL/min, give normal dose q 12 hr; if <10 mL/min, give q 24 hr.[13] The manufacturer recommends halving the dose when CrCl is <20 mL/min.[2]

Cefotaxime Sodium

Maximum dosage	300 mg/kg/day in neonates, infants, and children with meningitis.[9] Total daily dose should not exceed 12 g/day.[2]
Additives	Contains 2.2 mEq sodium/g of cefotaxime.[2]
Suitable diluents	D5W, D10W, NS, LR, D5NS, D5¼NS, D5½NS, sodium lactate injection (M/6) and 10% invert sugar injection [2,14]
Maximum concentration	200 mg/mL in SW for IV push.[2] 86 mg/mL in D5W, 73 mg/mL in NS, and 147 mg/mL in SW results in a recommended osmolality for peripheral infusion in fluid-restricted patients.[14,15]
Preparation and delivery	**Delivery system issues:** The mixing of cefotaxime with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[2] (See Appendix C for more specific information.) **Stability:** Satisfactory potency for 24 hours at or below 22°C, and at least 5 days under refrigeration (5°C).[2,14] Normal color is light yellow to amber; discoloration may suggest a loss of potency.[2,14] **Compatibility:** See Appendix D for PN compatibility information.[16] **Photosensitivity:** Protect from light.[14]
IV push	200 mg/mL over 3–5 minutes.[2,14] Rapid IV push (<1 minute) of a cephalosporin has caused potentially life-threatening arrhythmias.[2]
Intermittent infusion	10–40 mg/mL[2] over 20–30 minutes.[14]
Continuous infusion	May be used.[2]
Other routes of administration	230–330 mg/mL in BW may be given IM at same doses as IV.[2]
Comments	**Rare adverse effects:** Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics[2]; however, the literature is conflicted on this adverse effect.[17] Cephalosporins may inhibit vitamin K dependent clotting factors and may also suppress the gut flora that normally synthesize these clotting factors.[18] Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced.[2] If seizures associated with drug therapy occur, the drug should be discontinued and anticonvulsants should be given as indicated. **Monitor:** Signs and symptoms of *Clostridium difficile*–associated diarrhea. Because of the potential for nephrotoxicity, renal function should be carefully monitored, especially if large doses of the aminoglycosides are administered or if therapy is prolonged.[2] **Drug interactions:** Consult appropriate resources for dosing recommendations before combining any drug with cefotaxime. **Laboratory interference:** False–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used. Positive direct Coombs tests have been reported during treatment with cefotaxime.[2]

Cefotetan Disodium

Brand names	Cefotan
Medication error potential	USP reports confusion of cefotetan with cefamandole, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime and ceftriaxone.[1] Cefotan may be confused with Ceftin, cefazolin, cefepime, cefotaxime, cefoxitin, ceftriaxone, and Claforan.[1]
Contraindications and warnings	**Contraindications:** Should not be used in those with a known hypersensitivity reactions to cefotetan or another cephalosporin.[2] It is also contraindicated in those who have experienced cephalosporin-associated hemolytic anemia.[2] **Warnings:** Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins.[2] (See Appendix C for specific information.) Although rare, an immune-mediated hemolytic anemia, including fatalities, has been observed in patients receiving cephalosporins, especially cefotetan.[2] (See Comments section.) Cefotetan is associated with a decrease in prothrombin time and may lead to bleeding.[2] (See Comments section.) Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.[2]
Dosage	Doses and side effects have not been established in neonates, infants, and children. **Neonates:** No information. **Infants and children:** Inappropriate for mild-to-moderate infections.[3] For severe infections, 40–80 mg/kg/day divided q 12 hr up to 6 g/day.[3] **Adolescents and *adults*:** 2–6 g/day divided q 12 hr.[2] **Pelvic inflammatory disease:** 4 g/day divided q 12 hr (plus doxycycline 200 mg/day orally or IV divided q 12 hr) for at least 24 hours after the patient clinically improves.[3,4]
Dosage adjustment in organ dysfunction	Administer normal dose q 24 hr if CrCl is 10–29 mL/min and q 48 hr if CrCl is <10 mL/min.[2,5]
Maximum dosage	80 mg/kg/day[3]; 40 mg/kg/dose[3] up to 6 g/day in *adults*.[2]
Additives	3.5 mEq (80 mg) of sodium/g of cefotetan.[2,6]
Suitable diluents	D5W or NS.[2,6]
Maximum concentration	182 mg/mL for IV infusion and 500 mg/mL for IM administration.[2,6]

Cefotetan Disodium

Preparation and delivery	**Delivery system issues:** The mixing of cefotetan with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[2] (See Appendix C for more specific information.) Cefotetan in Galaxy plastic containers should not be used for IM administration.[2] **Stability:** Thawed solutions of the commercially available frozen cefotetan injections are stable for 48 hours at room temperature or 21 days when refrigerated.[2] Do not refreeze.[2] **Compatibility:** See Appendix D for PN compatibility information.[7]
IV push	≤182 mg/mL over 3–5 minutes.[2,6]
Intermittent infusion	≤40 mg/mL over 20–60 minutes.[6]
Continuous infusion	No information available to support cefotetan administration by this method; however, other beta-lactams have been given by continuous infusion.[8]
Other routes of administration	500 mg/mL in SW, BW, NS, 0.5, or 1% lidocaine by deep IM injection.[2 6] Should not be given IM to patients with septicemia, bacteremia, or life-threatening infections.[2]
Comments	**Rare adverse effects:** The risk of cefotetan-induced hemolytic anemia is 3 times higher than that reported with cephalosporins.[2] If anemia develops anytime within 2–3 weeks of receiving cefotetan, the diagnosis of a cephalosporin-associated anemia should be considered.[2] Cephalosporins may inhibit vitamin K–dependent clotting factors. Cefotetan may inhibit to a greater extent than other cephalosporins.[9] Patients with renal or hepatobiliary impairment or poor nutritional status, and those with cancer have an increased risk for cefotetan inhibition of vitamin K–dependent clotting factors.[2] **Monitoring:** Prothrombin time (especially if on warfarin) and administer exogenous vitamin K as needed.[2] Monitor for signs and symptoms of hemolytic anemia and *Clostridium difficile*–associated diarrhea. **Drug interactions:** Disulfiram-like reaction (flushing, sweating, headache, tachycardia) may occur when alcohol is consumed within 72 hours of administration of cefotetan.[2] **Laboratory interference:** Cefotetan may cause false–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, or Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used. When the Jaffe reaction is used to determine creatinine, high concentrations of cefotetan may cause falsely elevated serum or urinary creatinine values.[2] **Osmolality:** 200 mg/mL has an osmolarity of 800 mOsm/L.[6] Concentrations used for IM injection are very hypertonic and have osmolarities >1500 mOsm/L.[6]

Cefoxitin Sodium

Brand names	Mefoxin
Medication error potential	USP reports that cefoxitin sodium has been confused with cefazolin, cefepime, Cefotan, cefotaxime, cefotetan, ceftriaxone, and cefuroxime.[1]
Contraindications and warnings	**Contraindications:** In patients with known hypersensitivity to cefoxitin or to another cephalosporin antibiotic.[2] Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins. (See Appendix C for specific information.) **Warnings:** Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2] Antibiotic use that is not directed against *C. difficile* may need to be discontinued.[2]
Infusion-related cautions	If a decision is made to give this medication to a patient with known cephalosporin or penicillin hypersensitivity, the patient should be closely observed for allergenicity.[2] (See Appendix C for specific information.) Thrombophlebitis has been reported.[2]
Dosage	**Neonates:** Safety and efficacy in infants <3 months old have not been established.[2] Doses of 75–90 mg/kg/day divided q 8 hr have been reported.[3] **Infants and children** **Mild-to-moderate infections:** 80–100 mg/kg/day (up to 3–4 g/day) divided q 4–6 hr.[2,4,5] **Severe infections:** 80–160 mg/kg/day (up to 6–12 g/day) divided q 4–6 hr.[2,4–6] **Adolescents and *adults*:** 3–12 hr/day divided q 6–8 hr.[2] Dosage should be guided by susceptibility of organisms, severity of the infection, and clinical status of the patient. The larger dosages should be reserved for more severe or serious infections. **Pelvic inflammatory disease:** 8 g/day divided q 6 hr (plus doxycycline 100 mg orally or IV q 12 g) for at least 24 hours after the patient clinically improves.[4,7] **Surgical prophylaxis:** 30–40 mg/kg/dose (up to 1–2 g) given 30–60 minutes prior to surgery; followed by 120–160 mg/kg/day divided q 6 hr for no longer than 24 hours.[2]
Dosage adjustment in organ dysfunction	If CrCl is 30–50 mL/min give normal dose q 8 hr[8]; if CrCl is 10–29 mL/min, give normal dose q 12 hr[8]; if CrCl is <10 mL/min, give a normal dose q 24 hr[8]; if CrCl <5 mL/min, give 50% of a normal dose q 24–48 hr.[2]
Maximum dosage	160 mg/kg/day, not to exceed 12 g/day.[2] (See Comments section.)
Additives	2.3 mEq sodium/g of cefoxitin.[2,9] Some products may contain benzyl alcohol.[2] (See Appendix C for specific information about benzyl alcohol potential for toxicity.)
Suitable diluents	D5W, D10W, D5¼NS, D5½NS, D5NS, R, LR, D5LR, or NS.[2,9]
Maximum concentration	180 mg/mL for IV push,[2,9] and 40 mg/mL for IV infusion.[2] 112 mg/mL in SW results in a maximum recommended osmolality for peripheral infusion in fluid-restricted patients.[10]

Cefoxitin Sodium

Preparation and delivery	**Delivery system issues:** The manufacturer states that mixing of cefoxitin with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside although others have reported stability of the solutions.[2,9] (See Appendix C for more specific information.) **Compatibility:** See Appendix D for PN compatibility.[11]
IV push	180 mg/mL over 3–5 minutes.[2]
Intermittent infusion	10–40 mg/mL[2] over 15–40 minutes.[2,9]
Continuous infusion	10–40 mg/mL in D5W, NS, or D5NS.[2] Other beta-lactam antibiotics have been given by this method.[12]
Other routes of administration	None.
Comments	**Rare adverse effects:** Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside.[2] Large doses of cefoxitin have caused an increased incidence of eosinophilia and elevated aspartate aminotransaminase.[2] Several cephalosporins may cause seizures, particularly in significant renal impairment when the dosage was not reduced.[2,13,14] **Laboratory interference:** A false–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used. When the Jaffe reaction is used to determine creatinine, high concentrations of cefoxitin may falsely elevate serum or urinary creatinine values; hence, serum should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration.[2] A positive direct Coombs test may occur, especially those with azotemia.[2] High concentrations in the urine may interfere with determination of urinary 17-hydroxycorticosteroids by the Porter-Silber reaction and produce a false increase in the levels.[2]

Ceftaroline

Brand names	Teflaro
Medication error potential	None reported.
Contraindications and warnings	**Contraindications:** Ceftaroline is contraindicated in patients with known serious hypersensitivity to ceftaroline or other cephalosporins.[1] **Warnings:** Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[1] Hypersensitivity reactions have been reported. If allergic reactions occur ceftaroline should be stopped and appropriate measures taken.[1]
Infusion-related cautions	Phlebitis may occur.[1-3]
Dosage	**Ceftaroline has not been well studied in children. The following are pediatric doses currently being used in clinical trials:** **Infants and children (clinical trial)** **<6 months:** 30 mg/kg/day q 8 hr infused over 2 hours.[4] **≥6 months:** 45 mg/kg/day q 8 hr infused over 2 hours.[4] **>40 kg:** 1800 mg/day q 8 hr infused over 2 hours.[4] **Infants and children >2 months (clinical trials)** **≤33 kg:** 36 mg/kg/day divided q 8 hr infused over 1 hour.[5,6] **>33 kg:** 1200 mg/day divided q 8 hr infused over 1 hour.[5,6] ***Adults*:** 1200 mg/day divided q 12 hr.[1–3,7,8]
Dosage adjustment in organ dysfunction	If CrCl >30, give two-third of normal dose q 12 hr, if CrCl ≤30, give one-half of normal dose q 12 hr; if patient is in end-stage renal disease (including dialysis), give one-third of normal dose q 12 hr.[1]
Maximum dosage	1200 mg/day.[1]
Additives	None.
Suitable diluents	NS, D5W, D2.5W, ½NS, LR.[1]
Maximum concentration	12 mg/mL.[1]

Ceftaroline

Preparation and delivery	**Stability:** Diluted product is stable for 6 hours at room temperature and 24 hours under refrigeration.[1] **Compatibility:** The manufacturer recommends not mixing with other drugs.[1]
IV push	Not recommended.[1]
Intermittent infusion	Infuse over 1 hour.[1,5,6]
Continuous infusion	No information available.
Other routes of administration	None.
Comments	**Laboratory interference:** Direct Coombs test seroconversion has been reported with ceftaroline therapy.[3,9,10] If anemia occurs, a diagnostic workup should be done and ceftaroline may need to be stopped.[1]

Ceftazidime

Brand names

Fortaz, Tazicef

Medication error potential

Look-alike, sound-alike drug names.

USP reports that ceftazidime has been confused with cefazolin, cefepime, cefotaxime, cefotetan, ceftizoxime, ceftriaxone, cefuroxime and Maxipime.[1]

Contraindications and warnings

Contraindications: Should not be used in those with a known allergy to ceftazidime or another cephalosporin antibiotics.[2]

Warnings: Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins. Ceftazidime should be given cautiously to these patients.[2] (See Appendix C for specific information.)

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]

Infusion-related cautions

If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.[2]

Accidental intra-arterial administration has resulted in distal necrosis.[2]

Dosage

Neonates

PNA	<1200 g	≤2000 g	>2000 g
≤7 days	100 mg/kg/day divided q 12 hr[3]*	50–100 mg/kg/day divided q 12–18 hr[3–6]	100–150 mg/kg/day divided q 8–12 hr[3,5–7]
>7 days		150 mg/kg/day divided q 8 hr[3]	150 mg/kg/day divided q 8 hr[3,7]

*Until 4 weeks of age.

The manufacturer recommends 60 mg/kg/day divided q 12 hr for those 0–4 weeks of age.[2] 25 mg/kg q 24 hr has also been recommended for those <32 weeks gestational age.[8]

Infants and children

Mild-to-moderate infections: 75–100 mg/kg/day divided q 8 hr up to 3 g/day.[2,3]

Severe infections (including meningitis): 125–150 mg/kg/day divided q 8 hr up to 6 g/day.[2,3,9–13]

Adolescents and *adults*: 2–3 g/day divided q 8–12 hr up to 6 g/day.[2,3] Dose is dependent on type and severity of infection.[2]

The larger doses should be reserved for patients with cystic fibrosis (CF), meningitis, or those who are immunocompromised.

CF: 150–400 mg/kg/day divided q 6–8 hr.[14–19]

Neutropenia and fever (empiric therapy): 100–150 mg/kg/day divided q 6–12 hr as monotherapy.[11,12,20,21]

Ceftazidime

Dosage adjustment in organ dysfunction	If CrCl is 31–50 mL/min, give normal dose q 12 hr; if CrCl is 16–30 mL/min, give q 24 hr[2]; if CrCl is 6–15 mL/min, give 50% of the normal dose q 24 hr[2]; and if CrCl is <5 mL/min, give 50% of the normal dose q 48 hr.[2] Another reference recommends a dose of 50 mg/kg q 12 hr if CrCl is 30–50 mL/min, a dose of 50 mg/kg q 24 hr if CrCl is 10–29 mL/min, and a dose of 50 mg/kg q 48 hr if CrCl is <10 mL/min.[22] No dosage adjustment necessary in hepatic dysfunction.[2]
Maximum dosage	320 mg/kg/day in patients with CF,[16] not to exceed 6 g/day.[2,7,23]
Additives	Contains 2.3 mEq sodium/g of ceftazidime.[2,24]
Suitable diluents	D5W, D10W, LR, NS, D5NS, D5¼NS, D5¼NS, D5½NS, ⅙M sodium lactate injection, or Normosol-M.[2,24]
Maximum concentration	170 mg/mL.[2] 125 mg/mL in SW results in a maximum recommended osmolality for peripheral infusion in fluid-restricted patients.[25]
Preparation and delivery	**Delivery system issues:** The mixing of ceftazidime with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[2] (See Appendix C for more specific information.) When ceftazidime is reconstituted, carbon dioxide is produced, resulting in bubbles and positive pressure in the vial.[2] The pressure is reduced by removing air from the vial with a syringe.[2] Bubbles remaining in the solution must be expelled prior to infusion.[2] **Stability:** Variable stability based on diluents and storage conditions. See manufacturer information[2] or specialty reference.[24] Once thawed, solutions should not be refrozen.[2] **Compatibility:** See Appendix D for PN compatibility information.[26]
IV push	100–170 mg/mL in SW over 3–5 minutes.[2]
Intermittent infusion	1–40 mg/mL infused over 15–30 minutes.[2]
Continuous infusion	Although concentration and solution type are usually not specified, ceftazidime has been given by this method.[27,28] 200 mg/kg in 100 mL D5W has been given over 24 hours to febrile neutropenic children.[28] 100 mg/kg/day have been given by continuous infusion to CF patients.[29]
Other routes of administration	280 mg/mL may be given IM in SW, BW, 0.5% and 1% lidocaine hydrochloride.[2]

Ceftazidime

Comments

Rare adverse effects: Although nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics, the literature is conflicted on this adverse effect.[30]

Biliary sludging has been reported in a neonate.[31]

Many cephalosporins may decrease in prothrombin activity.[2,4,32] Patients with renal or hepatobiliary impairment or poor nutritional status, and those with cancer have an increased risk for this adverse effect.[2] Prothrombin time should be monitored in patients at risk, and exogenous vitamin K administered as indicated.[2]

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced.[2] If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Monitor: CBC, prothrombin time (especially if on warfarin); signs and symptoms of *Clostridium difficile*–associated diarrhea. Because of the potential for nephrotoxicity, renal function should be carefully monitored, especially if large doses of the aminoglycosides are administered or if therapy is prolonged.[2]

Drug interactions: Cephalosporins may enhance the anticoagulant effect of vitamin K antagonists (e.g., warfarin).[2] May need to adjust dosage in premature neonates receiving indomethacin[33,34] Concomitant administration of cephalosporins with an aminoglycoside or potent diuretics (e.g., furosemide) may increase the likelihood of nephrotoxicity.[2] Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone.[2] Other interactions may occur; consult appropriate resources for dosing recommendations before combining any drug with ceftazidime.

Laboratory interference: False–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used.[2] Positive direct Coombs tests have been reported during treatment with ceftazidime.[2]

CefTRIAXone Sodium

Brand names

Rocephin

Medication error potential

ISMP recommends the following tall man letters (not FDA approved) to decrease confusion between ceFAZolin and cefTRIAXone.[1]

Look-alike, sound-alike drug names.

USP reports that cefTRIAXone sodium has been confused with cefazolin, cefepime, Cefotan, cefotaxime, cefotetan, cefoxitin, ceftazidime, and cefuroxime.[2] Rocephin may be confused with cefazolin and Robaxin.[2]

Contraindications and warnings

Contraindications: Should not be used in those with a known allergy to cefTRIAXone or another cephalosporin antibiotics.[3] CefTRIAXone can displace bilirubin from its binding sites on serum albumin and may cause kernicterus and encephalopathy in hyperbilirubinemic neonates, especially premature neonates.[3]

CefTRIAXone must not be co-administered with calcium-containing IV solutions (e.g., Ringer's solution, Hartmann's solution, and PN formulations that contain calcium) in neonates because of the risk of precipitation of cefTRIAXone–calcium salt.[3] Cases of fatal reactions with cefTRIAXone–calcium precipitates in lungs and kidneys in neonates have been described.[3,4] In some cases the infusion lines and the times of administration of cefTRIAXone and calcium-containing solutions differed.[3,4] CefTRIAXone and products that contain calcium may be administered sequentially to patients outside the neonatal period, as long as the infusion lines are thoroughly flushed between infusions with a compatible fluid.[3] CefTRIAXone should not be administered simultaneously with any calcium-containing solution via Y-site in any patient.[3]

Warnings: Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins. CefTRIAXone should be given cautiously to these patients.[3] (See Appendix C for specific information.)

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[3]

Infusion-related cautions

If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.

Dosage

Neonates[5]: See Contraindications and Warnings section.

PNA	<1200 g	≤2000 g	>2000 g
≤7 days	50 mg/kg q 24 hr*	50 mg/kg q 24 hr	50 mg/kg q 24 hr
>7 days		50 mg/kg q 24 hr	50–75 mg/kg q 24 hr

*Until 4 weeks of age.

Infants and children

Non-CNS infection: 50–75 mg/kg/day given as a single dose or divided q 12 hr, up to 2 g/day.[3,5,6]

CNS infection: 80–100 mg/kg/day given as a single dose or divided q 12 hr, up to 4 g/day.[3,5,7–13]

Dosage *(cont.)*	**Gonococcal infection** **Complicated:** 50 mg/kg/day (up to 1 g/day) as a single dose for 7 days.[5,14] If meningitis or endocarditis, give 50 mg/kg/day (up to 2 g/day) divided q 12 hr for 10–14 days and 28 days, respectively, plus erythromycin.[5,14] **Ophthalmia:** Neonates born to mothers with known untreated gonorrhea should receive 25–50 mg/kg (up to 125 mg) as a single dose IV/IM.[5] **Prophylaxis:** Neonates born to mothers with gonococcal infections should be given 25–50 mg/kg (up to 125 mg) as a one-time dose.[5,14] Regardless of weight, children should receive 125 mg IM.[5] If providing prophylaxis after sexual victimization, add appropriate therapies for chlamydia trachomatis, hepatitis B, and trichomoniasis.[5,14] **Uncomplicated:** If ≤45 kg give 125 mg, if >45 kg give 250 mg as a single dose IM plus a macrolide antibiotic.[5,14] **Otitis media:** 50 mg/kg (up to 1 g) as a single dose. Generally administered IM.[15–17]
Dosage adjustment in organ dysfunction	Most patients with renal dysfunction who receive ≤2 g/day do not require dosage adjustment.[3,18,19] However, some patients with end-stage renal disease receiving hemodialysis may accumulate cefTRIAXone.[3,19] It is recommended that patients with a GFR <10 receive their dose every 24 hours only.[18] No adjustment in hepatic dysfunction; however, if both hepatic and renal dysfunction the dosage should not exceed 2 g/day.[3]
Maximum dosage	100 mg/kg/day,[3,5] not to exceed 4 g/day.[3,5]
Additives	Contains 3.6 mEq sodium/g of cefTRIAXone.[3,20]
Suitable diluents	D5NS, D5½NS, D5W, D10W, NS, or SW. Compatibility varies for dextrose–saline combinations. See more specific reference.[3]
Maximum concentration	40 mg/mL for IV administration and 350 mg/mL for IM use.[3]
Preparation and delivery	**Stability:** Do not force thaw by immersion in water baths or by microwave irradiation.[3] 250 and 350 mg/mL reconstituted solutions are stable for 24 hours at room temperature and for 72 hours if refrigerated.[3,20] 100 mg/mL for 48 hours at room temperature and for 10 days if refrigerated.[3,20] **Compatibility:** See Appendix D for PN compatibility information.[21] **Photosensitivity:** Protect from light before reconstitution.[20]
IV push	10–40 mg/mL.[3,20] Although infusion over 30 minutes is now recommended[3] doses have been given over 2–3 minutes in ambulatory patients >11 years of age[22], over 5 minutes in children with meningitis[10] and 10–15 minutes in serious bacterial infections in children.[23] Ten minutes after cefTRIAXone. was infused over 5 minutes, an *adult* being treated for presumed meningitis became diaphoretic, hypertensive, and tachycardic and developed palpitations.[24] Subsequent infusions over 30 minutes were uneventful.[24] Cholelithiasis has been reported to occur more frequently with bolus infusions in children [25,26]
Intermittent infusion	10–40 mg/mL[3,20] infused over 30 minutes.[3]

CefTRIAXone Sodium

Continuous infusion	No specific information is available to support administration by this route.
Other routes of administration	100–350 mg/mL in SW, NS, D5W, BW, or 1% lidocaine (without epinephrine) by deep IM injection.[3,20]
Comments	**Rare adverse effects:** Although nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics, the literature is conflicted on this adverse effect.[27] CefTRIAXone has been reported to cause primary cholelithiasis,[3,25,28] nephrolithiasis,[29] and hemolytic anemia.[30] Gallstones spontaneously resolved after discontinuation of the drug.[25,26,28] Cases of pancreatitis, possibly secondary to biliary obstruction, have been reported rarely in patients treated with cefTRIAXone.[3] Alterations in prothrombin times have occurred rarely in patients treated with cefTRIAXone.[3,31] Patients with impaired vitamin K synthesis or low vitamin K stores (e.g., chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during treatment. Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced.[32] If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated. **Monitor:** CBC, prothrombin time (especially if on warfarin); signs and symptoms of *Clostridium difficile*–associated diarrhea.[3] **Laboratory interference:** CefTRIAXone false–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[3] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used.[3] Positive direct Coombs, lactate dehydrogenase, and urinary glucose tests have been reported during treatment with cefTRIAXone.[3]

Cefuroxime Sodium

Brand names	Zinacef
Medication error potential	Look-alike, sound-alike drug names. USP reports that cefuroxime sodium has been confused with cefadroxil, cefazolin, cefepime, cefotaxime, cefoxitin, ceftazidime, ceftizoxime, ceftriaxone, and cephalexin.[1] USP reports confusion for Zinacef with Zithromax.[1]
Contraindications and warnings	**Contraindications:** Should not be used in those with a known allergy to cefuroxime or another cephalosporin antibiotics.[2] **Warnings:** Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins. Cefuroxime should be given cautiously to these patients.[2] (See Appendix C for specific information.) Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.[2] Thrombophlebitis may occur.[2]
Dosage	**Neonates:** Safety and efficacy in infants <3 months old have not been established.[2] However, 50 mg/kg q 12 hr has been used in the most premature neonates. Frequency of dosing has been adjusted based on postnatal age.[3,4] **Infants ≥3 months and children** **Mild-to-moderate infections:** 50–100 mg/kg/day divided q 6–8 hr.[2,5–10] **Severe infections:** 100–150 mg/kg/day divided q 8 hr.[5] Cefuroxime should not be used to treat bacterial meningitis. (See Comments section.) **Surgical prophylaxis (clean-contaminated or potentially contaminated procedures):** In *adults* the manufacturer recommends that a dose of 1.5 g be given 30–60 minutes before surgery to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure.[2] The dose should be repeated intraoperatively if the surgical procedure is lengthy (750 mg/dose q 8 hr).[2]
Dosage adjustment in organ dysfunction	Adjust dosage in patients with renal dysfunction.[2,11] If CrCl is 10–20 mL/min, give a normal dose q 12 hr, and if CrCl is <10 mL/min, give q 24 hr.[2,11]
Maximum dosage	300 mg/kg/day,[12,13] not to exceed 6 g/day in children[5] and 3 g/dose or 9 g/day in *adults* with meningitis.[2]
Additives	Contains 2.4 mEq sodium/g of cefuroxime.[2,14]
Suitable diluents	D5W, D10W, NS, LR, D5NS, D5¼NS, D5½NS, R, ⅙M sodium lactate.[2,14]

Cefuroxime Sodium

Maximum concentration	90 mg/mL for IV push and 225 mg/mL for IM administration.[2] 137 mg/mL in SW (489 mOsm/kg) resulted in a maximum recommended osmolality for peripheral infusion in fluid-restricted patients.[15]
Preparation and delivery	**Delivery system issues:** The mixing of cefuroxime with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside. (See Appendix C for more specific information.) **Stability:** Stable for 24 hours at room temperature and 2–28 days if refrigerated depending on formulation.[2,14] **Compatibility:** See Appendix D for PN compatibility information.[16]
IV push	90 mg/mL[2] over 3–5 minutes.[2,14]
Intermittent infusion	≤30 mg/mL[2,14] over 15–60 minutes.[14]
Continuous infusion	In D5W, D10W, NS, D5NS, D5½NS, or ⅙M sodium lactate injection.[2]
Other routes of administration	225 mg/mL reconstituted with SW and administered into large muscle mass (gluteus or lateral thigh).[2,14]
Comments	**Rare adverse events:** Infants and children with meningitis who were treated with cefuroxime had an increased incidence of hearing loss[13,17] and an increased time to sterilization of their cerebrospinal fluid.[17] The AAP does not recommend cefuroxime for meningitis.[5] Although nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics,[2] the literature is conflicted on this adverse effect.[18] Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced.[2] If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated. Cephalosporins may inhibit vitamin K–dependent clotting factors.[19] Patients with renal or hepatobiliary impairment or poor nutritional status have an increased risk for this adverse effect.[2] (See Appendix C for specific information.) **Monitor:** CBC, prothrombin time (especially if on warfarin); signs and symptoms of *Clostridium difficile*–associated diarrhea. Although rare, cefuroxime may produce alterations in kidney function[2]; hence, evaluation of renal function is recommended, especially in seriously ill patients receiving large doses. **Drug interactions:** Concomitant use of probenecid decreases tubular secretion and may increase serum concentrations of cefuroxime.[2] Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics (e.g., furosemide) as these may negatively affect renal function.[2] In common with other antibiotics, cefuroxime may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined estrogen/progesterone oral contraceptives.[2] **Laboratory interference:** A false–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used.[2] Positive direct Coombs tests have been reported during treatment with cefuroxime.[2] Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.[2]

Chloramphenicol Sodium Succinate

Brand names	Chloromycetin
Medication error potential	None reported.
Contraindications and warnings	**U.S. boxed warning:** Serious and fatal blood dyscrasias (aplastic anemia terminating in leukemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) have occurred with both short- and long-term use.[1] **Contraindications:** Should not be used in individuals with a history of previous hypersensitivity and/or toxic reaction to chloramphenicol.[1] It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.[1] **Other warnings:** Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[1] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[1]
Infusion-related cautions	None reported.
Dosage	Inappropriate for mild-to-moderate infections.[1,2] Dosing should be optimized by measuring serum chloramphenicol concentrations.[1–3] **Neonates (see Comments section)** **Loading dose:** Loading dose of 20 mg/kg followed in 12 hours by maintenance doses.[4] **Maintenance dose:** Although the manufacturer recommends 25 mg/kg/day divided q 6 hr,[1] most sources recommend more conservative dosing in neonates.[3–11] **Premature, ≤1200 g:** 22 mg/kg q 24 hr.[6] **Premature, ≤2000 g and ≤1 week:** 25 mg/kg q 24 hr.[6] **Term, <2 weeks:** 25 mg/kg/day divided q 12 hr.[3,5, 7–11] **Term, 2–4 weeks:** 25–50 mg/kg/day divided q 12 hr.[3,5,7–11] **Infants and children:** 50–100 mg/kg/day divided q 6–8 hr.[1,2,5,8–20] Because of the emergence of vancomycin-resistant *Enterococcus*, some have recommended 75–100 mg/kg/day divided q 6 hr for the treatment of meningitis.[18–21] Other investigators noted that 100 mg/kg/day may be unnecessary and only increases the incidence of toxicity.[5,14,15] Larger dosage, which may be required for severe infections, should only be given to maintain the serum chloramphenicol concentration within a "therapeutic" range.[1]
Dosage adjustment in organ dysfunction	Adjust dosage in patients with hepatic[8–11] or renal[21,22] dysfunction. Dosage should be adjusted based on serum chloramphenicol concentrations.[1]
Maximum dosage	100 mg/kg/day.[2,8,10,11] In neonates <2 weeks of age, 25 mg/kg/day[1,23] and 50 mg/kg/day in neonates <4 weeks of age.[1,24] Maximum *adult* dose should not exceed 2–4 g/day.[1] When large doses are used, serum concentration monitoring is imperative.
Additives	Contains 2.25 mEq (52 mg) sodium/g of chloramphenicol sodium succinate.[25]

Chloramphenicol Sodium Succinate

Suitable diluents	D2.5W, D5W, D10W, NS, ½NS, LR, D5LR, D5NS.[25]
Maximum concentration	100 mg/mL.[25]
Preparation and delivery	**Stability:** Activity is retained for 24 hours at pH 3.6–7.5 in D5W.[25] **Compatibility:** See Appendix D for PN compatibility information.[26]
IV push	100 mg/mL over ≥1 minute.[1]
Intermittent infusion	20–25 mg/mL over 15–60 minutes.[6,17,25]
Continuous infusion	Although concentration and solution type were not provided, chloramphenicol has been given by this method.[27]
Other routes of administration	Can be administered IM,[1,23] but the drug may be less effective.[23] Has been administered intraventricularly in an *adult*.[28]
Comments	**Significant adverse events:** Fatalities associated with gray syndrome (e.g., abdominal distension, progressive pallid cyanosis, circulatory collapse, acidosis, and myocardial depression) may result from drug accumulation in patients with immature or impaired hepatic or renal function.[29–33] Because it is generally associated with serum concentrations >50 mg/L, individualize dosage based on serum concentrations. **Monitoring:** Hematological studies, which should be obtained at baseline and repeated every 2 days, are essential and may detect early peripheral blood changes.[1] The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia or any other blood study findings attributable to chloramphenicol. However, normal blood tests do not exclude the possibility of later appearance of the irreversible type of bone marrow depression.[1] Serum chloramphenicol concentrations should be collected 90 minutes after completion of the IV dose (peak) and immediately prior to the next dose (trough). Dose adjustments should be based on desired serum chloramphenicol concentrations nonmeningitis (peak: 10–20 mg/L; trough: 5–10 mg/L) and meningitis (peak: 15–25 mg/L; trough: 5–15 mg/L).[34] **Drug interactions:** Chloramphenicol inhibits the metabolism of several drugs (e.g., phenytoin, phenobarbital, tolbutamide, dicumarol, cyclosporine, and tacrolimus).[35–37] Likewise, many drugs (e.g., rifampin, phenobarbital, and phenytoin) decrease chloramphenicol concentrations. Consult appropriate resources for dosing recommendations before combining any drug with chloramphenicol.

Chlorothiazide

Brand names	Diuril, generics
Medication error potential	USP reports chlorothiazide has been confused with chloral hydrate and chlorthalidone. Diuril has been confused with Diamox.[1]
Contraindications and warnings	**Contraindications:** Anuria. Contraindicated if hypersensitive to components or sulfonamides.[2] **Warnings:** Use with caution in severe renal disease or hepatic disease.[2]
Infusion-related cautions	Extravasation may occur.[2]
Dosage	IV use in infants and children has not been well studied.[2,3] The manufacturer states that IV and oral dosing regimens are equivalent[2,7] although smaller IV doses have typically been used. **Infants** **Central diabetes insipidus:** 10–15 mg/kg/day divided q 8–12 hr IV has been used.[4] **Hyperinsulinemic hypoglycemia:** 7–10 mg/kg/day divided q 12 hr IV has been used.[5,6] **Children (ORAL DOSING)** **6 months–12 years old**: 10–20 mg/kg/day ORALLY divided q 12–24 hr, not to exceed 375 mg/day in children less than 2 years old and 1000 mg/day in children 2–12 years old.[7,8]
Dosage adjustment in organ dysfunction	When CrCl ≥30 mL/min, give normal dose.[9] Thiazide diuretics are not effective when CrCl <30 mL/min.[9] The manufacturer warns that cumulative effects may been seen in those with impaired renal function.[2]
Maximum dosage	Up to 25 mg/kg/day has been reported in a 2 year old.[10]
Additives	Each vial of 50 mg contains approximately 2.5 mEq sodium.[11]
Suitable diluents	D5W, NS.[2]
Maximum concentration	28 mg/mL.[2,7]
Preparation and delivery	**Preparation:** Reconstitute only with SW.[2,7] **Delivery:** May be given slowly by direct IV injection or by IV infusion.[2] **Stability:** Use immediately after preparation.[2]
IV push	May be given slowly by direct IV injection.[2]

Chlorothiazide

Intermittent infusion	May be given by IV infusion.[2]
Continuous infusion	None reported.
Other routes of administration	Do not give SC or IM.[2]
Comments	**Rare adverse effects:** Exacerbation or potentiation of systemic lupus erythematosus has been reported. Hyperuricemia or gout may be precipitated.[2] **Monitoring:** Patients should be monitored for fluid or electrolyte imbalance.[2] **Drug interactions:** Diuretics decrease the clearance of lithium. Antidiabetic drug dosages may need adjusted.[2] **Laboratory interference:** Thiazides should be discontinued before testing for parathyroid function.[2]

ChlorproMAZINE HCl

Brand names	Thorazine, generic
Medication error potential	Look-alike, sound-alike drug names. ISMP reports that chlorproMAZINE has been confused with chlordiazepoxide and chlorpropamide. USP also reports that chlorproMAZINE has been confused with chlordiazepoxide (no patient harm resulted) and chlorpropamide (patient harm resulted).[1] USP also reports that chlorproMAZINE has been confused with carbamazepine, chlorthalidone, clomipramine, Compazine, cyclobenzaprine, perphenazine, prochlorperazine, and thioridazine; no patient harm resulted.[2] USP reports that Thorazine has been confused with thiamine, thioridazine, and trazodone; no patient harm resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** ChlorproMAZINE carries warnings for QT interval prolongation and increased mortality in elderly patients with dementia-related psychosis.[3] **Contraindications:** Known hypersensitivity to the drug, use in comatose patients, concomitant large doses of CNS depressants.[3] **Other warnings:** Do not use in children <6 months of age, except where potential exists to save the child's life.[3]
Infusion-related cautions	Systemic hypotension has occurred in neonates.[4] Because of the risk of hypotension, patients should continue to lie down for 30 minutes after the injection.[3] Thrombophlebitis may occur.[5]
Dosage	**Nausea and vomiting:** 0.5–1 mg/kg IM/IV q 6–8 hr PRN.[3,6] **During surgery** **IM:** 0.275 mg/kg; if nausea and vomiting persist after 30 minutes and hypotension has not occurred, the regimen may be repeated.[3] **IV:** 1 mg at 2-minute intervals up to a total dose of 0.275 mg/kg; do not exceed IM dosage.[3] **Neonatal abstinence syndrome/withdrawal:** While phenobarbital is preferred, IM chlorproMAZINE has been used for this indication. If used, initial IM doses range from 0.5–0.7 mg/kg q 6 hr for up to 4 days, then dose should be changed to oral route and decreased gradually over 2–3 weeks.[6] ChlorproMAZINE 0.5 mg/kg q 6 hr has been used to treat neonatal withdrawal after in utero selective serotonin reuptake inhibitor (SSRI) exposure.[5] **Presurgical apprehension:** 0.5 mg/kg IM 1–2 hours before surgery.[3] **Sedation for imaging:** For infants and children, 0.5 mg/kg 45 minutes prior to scan.[7] **Severe behavioral problems:** 0.5–1 mg/kg IM q 6–8 hr PRN; for severe disorders, larger doses may be necessary; start low and increase gradually up to maximum doses (see Maximum Dosage section); older patients may require 200 mg or more daily (further behavior improvement not seen with doses >500 mg/day).[3,6] **Tetanus:** 0.5 mg/kg IM/IV q 6–8 hr.[4]
Dosage adjustment in organ dysfunction	Although one reference suggests that no dosage adjustment is necessary in renal dysfunction,[8] the manufacturer recommends chlorproMAZINE be administered cautiously in patients with renal disease.[3] It should also be used cautiously in patients with cardiovascular, liver, or chronic respiratory disease.[3]

ChlorproMAZINE HCl

Maximum dosage	**6 months–5 years or <23 kg:** 40 mg/day.[3,6] **5–12 years or 23–45 kg:** 75 mg/day.[3,6]
Additives	**1- and 2-mL ampules (25 mg/mL chlorproMAZINE) contain per mL:** 2 mg ascorbic acid, 1 mg sodium metabisulfite, 6 mg sodium chloride, and 1 mg sodium sulfite.[3,9] See Appendix C for more specific information about potential adverse effects of sulfites.
Suitable diluents	NS, ½NS, D2.5W, D5W, D10W, LR, R, D–LR combinations, D–R combinations, D-saline combinations.[3,9]
Maximum concentration	1 mg/mL.[9]
Preparation and delivery	See Appendix D for PN compatibility information.
IV push	Dilute to ≤1 mg/mL in NS[3,18] not to exceed 0.5 mg/min in children and 1 mg/min in *adults.*[3,9]
Intermittent infusion	Dilute to ≤1 mg/mL in NS[3,18] not to exceed 0.5 mg/min in children and 1 mg/min in *adults*.[3,9]
Continuous infusion	Not reported.
Other routes of administration	May be given via IM injection. Inject slowly, deep into large muscle.[3] If irritation is a problem, dilute with NS or 2% procaine.[3,9] SC injection not recommended.[3,9]
Comments	**Significant adverse effects:** An association has been found between chlorproMAZINE use and acute and clinically relevant liver injury.[10] **Drug interactions:** Because chlorproMAZINE is associated with several drug interactions, consult appropriate resources for dosing recommendations before combining any drug with chlorproMAZINE.[3] **Other:** Meperidine, promethazine, and chlorproMAZINE have been used in combination (Demerol, Phenergan, Thorazine [DPT] cocktail) to sedate pediatric patients.[11–15] However, with the availability of safer and more effective agents,[13,16–17] this combination is no longer recommended.[15] In one study in *adults*, incremental IV administration of 12.5 mg to a maximum of 37.5 mg was as effective as sumatriptan for the pain of acute migraine.[18] Larger doses (4.6 ± 1.8 mg/kg) have been used for systemic vasodilation during cardiopulmonary bypass in neonates.[19] ChlorproMAZINE poisoning (17 mg/kg up to 100 mg/kg) has occurred in children; ingestions in children of ≤15 mg/kg producing clinical effects or >15 mg/kg should be referred to the hospital for therapy.[20]

Cimetidine

Brand names	Tagamet, generic
Medication error potential	Look-alike, sound-alike drug names. USP reports that cimetidine has been confused with amantadine and that Tagamet has been confused with Tegretol.[1]
Contraindications and warnings	Known hypersensitivity to the drug.[2]
Infusion-related cautions	In *adults*, rapid administration over 1–5 minutes has resulted in cardiac dysrhythmias,[3] hypotension,[4,5] and cardiac arrest,[6] particularly in individuals with myocardial disease.
Dosage	**Premature neonates:** 8–10 mg/kg/day divided q 6–12 hr.[7–9] **Term neonates:** 8–24 mg/kg/day divided q 6–12 hr. [8,10–13] **Infants and children:** 20–40 mg/kg/day up to 1.2 g divided q 4–6 hr.[14–20] In *adults*, a loading dose of 150–300 mg infused over ≥5 minutes has been followed by a continuous infusion of 37.5–100 mg/hr diluted in a compatible fluid.[21–23] (See Maximum Dosage section.)
Dosage adjustment in organ dysfunction	Adjust dosage in patients with severe renal dysfunction.[2,24] If CrCl <30 mL/min, give 50% of normal dose.[2] Dosage adjustment may also be necessary in hepatic impairment.[2]
Maximum dosage	40 mg/kg/day,[14–17] not to exceed 2.4 g/day in *adults*.[2]
Additives	Multidose vials contain benzyl alcohol 0.9% as a preservative.[2,25] See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates. Also available in a premixed solution in NS, which contains 7.7 mEq sodium per 50 mL.[25]
Suitable diluents	Most commonly used solutions including D5W, D10W, LR, NS, and sodium bicarbonate 5%.[25]
Maximum concentration	15 mg/mL for slow IV push, 6 mg/mL for IV infusion.[2,25] 150 mg/mL for IM injection.[2,25]
Preparation and delivery	Visually compatible with PN and stable in PN and TNA solutions for 24 hours at room temperature.[25–27] See Appendix D for additional PN compatibility information.
IV push	15 mg/mL[2,25] has been infused over no less than 5 minutes.[2,4,6,16,25,28] (See Infusion-Related Cautions section.)

Cimetidine

Intermittent infusion	6 mg/mL[26] infused over 15–20 minutes.[2,25]
Continuous infusion	6 mg/mL in 100–1000 mL of suitable diluent.[25]
Other routes of administration	150 mg/mL (undiluted) may be given IM.[25]

Comments

Significant adverse effects: Reversible confusional states have been observed in *adults*.[2]

Reversible cerebral toxicity (inattention, lack of spontaneous movements, no crying, and decreased ability to track objects or respond to verbal stimuli) has been reported in a 2-month-old infant receiving 40 mg/kg/day.[29] These effects did not reappear at doses of 25 mg/kg/day.

A 4-year-old child on 15 mg/kg/day of cimetidine in combination with two other CNS-active drugs was reported to have dysarthria, hallucinations, and was picking at bedclothes.[30]

Cimetidine has been associated with hypoxemia in a neonate receiving concomitant tolazoline therapy.[31]

Pharmacokinetic considerations: Clearance is increased in children with burns,[18,32] cystic fibrosis,[33] or critical illness.[15,17]

Drug interactions: Cimetidine inhibits a variety of CYP isoenzymes and is associated with numerous drug interactions.[2] Consult appropriate resources for dosing recommendations before combining any drug with cimetidine.

Other: The use of H2-blocker therapy has been associated with the incidence of necrotizing enterocolitis in very low birth weight infants.[34,35]

Ciprofloxacin Lactate

Brand names	Cipro IV
Medication error potential	USP reports that ciprofloxacin lactate has been confused with cephalexin, gatifloxacin, levofloxacin, and moxifloxacin; there also has been confusion of Cipro with Ceftin and Cleocin.[1]
Contraindications and warnings	**U.S. boxed warning:** Fluoroquinolones are associated with an increased risk of tendinitis and tendon rupture in all ages.[2] This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroids, and in patients with kidney, heart, or lung transplants.[2] **Contraindications:** In persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobials, or any of the product components.[2] Concomitant administration with tizanidine is contraindicated.[2] Because arthropathy has been noted in immature animals given fluoroquinolones the package insert states that ciprofloxacin should only be used in children <18 with complicated urinary tract infections and pyelonephritis (not first line) and inhalational anthrax.[2] (See Rare Adverse Effects in the Comments section.) **Other warnings:** Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported. Ciprofloxacin should be discontinued if (1) symptoms of neuropathy (e.g., pain, burning, tingling, numbness, and/or weakness) are present, and (2) the patient develops deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.[2] Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	Anaphylaxis has occurred after the first dose[2–4] and may be accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching.[2] Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, IV fluids, IV antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.[2] Thrombophlebitis, burning, pain, erythema, and swelling occur more frequently when infusion time is <30 minutes.[2,5]
Dosage	The AAP recommends that ciprofloxacin is not appropriate in mild-to-moderate infections.[6] **Neonates:** A recent systematic review has reported doses ranging from 10–60 mg/kg/day, typically divided BID, in term and preterm neonates. Most regimens ranged from 10–20 mg/kg/day divided BID. No serious adverse effects were reported.[7] **Infants and children** **Mild-to-moderate infections:** Inappropriate.[6] **Severe infections:** 18–30 mg/kg/day divided q 8–12 hr up to 400 mg q 8–12 hr.[2,6] Some patients with sepsis may require 30 mg/kg/day divided q 8 hr.[8] An infant with ventriculitis was given 35 mg/kg/day divided q 12 hr for 4 doses.[9] These doses resulted in an unacceptable increase in serum concentrations and the dosage was decreased (25 mg/kg/day divided q 12 hr) and continued for 21 days.

Dosage *(cont.)*	**Biologic warfare or bioterrorism:** The CDC and other experts recommend that treatment of inhalational anthrax spores due to biologic warfare or bioterrorism should be started on a multiple-drug parenteral regimen that includes ciprofloxacin (10–15 mg/kg/dose q 12 hr for 60 days; do not exceed 1 g/day). Patients should be switched to oral therapy when clinically appropriate.[2,10,11] **Burns:** Children with burn or burn-type wound infections have been given 20–30 mg/kg/day (interval not provided) for 7–10 days and had no radiographic evidence of arthropathy.[12] **Cystic fibrosis:** 20–30 mg/kg/day divided q 8–12 hr up to 1.2 g/day.[13–15] Two pharmacokinetic studies in children with cystic fibrosis recommend dosages of 20–30 mg/kg/day divided q 8–12 hr.[14,15] **Typhoid fever:** Eighteen children with severe typhoid fever were given 10 mg/kg/day divided q 12 hr initially and then changed to oral therapy as tolerated.[16] The total duration of therapy was 7–14 days. In a separate study, 16 children received doses ranging from 7–24 mg/kg/day; all but one were eventually changed to oral therapy.[17]
Dosage adjustment in organ dysfunction	If CrCl is >30 mL/min, give at normal dosing interval; if CrCl is 10–29 mL/min, dose q 18 hr, if CrCl <10 mL/min, dose q 24 hr.[2,18] No adjustment required for chronic stable liver dysfunction.[2]
Maximum dosage	1200 mg/day divided q 8 hr in *adults*.[2]
Additives	None.
Suitable diluents	D5W, D10W, NS, SW, RL, D5¼NS, D5½NS.[19]
Maximum concentration	2 mg/mL.[2]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.[20]
IV push	Not recommended.[2]
Intermittent infusion	0.5–2 mg/mL over 60 minutes.[2,19] (See Infusion-Related Cautions section.)
Continuous infusion	Not administered by this method.
Other routes of administration	None.

Ciprofloxacin Lactate

Comments

Rare adverse events: Several investigators were unable to prove ciprofloxacin-induced arthropathy in pediatric patients following IV or oral dosing.[21–25] Two retrospective safety studies of 1795[26] and >1700[25] children report arthralgia rates of 1.5% and 0%, respectively. An extensive review of the issue has been published.[27]

The Committee on Infectious Diseases of the AAP states that ciprofloxacin seems to be well tolerated and does not appear to cause arthropathy.[6] Use of ciprofloxacin in pediatric patients is justifiable if no other agent is available,[2] and infection is caused by multidrug-resistant, gram-negative, enteric, or one of several other pathogens.[21]

Serious and sometimes fatal hypersensitivity events have been reported.[2–5] These generally occur following multiple doses and manifestations as one or more of the following: (1) fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome); (2) vasculitis, arthralgia, or myalgia; (3) serum sickness; (4) allergic pneumonitis; (5) interstitial nephritis, acute renal insufficiency or failure; (6) hepatitis, jaundice, acute hepatic necrosis or failure; and (7) anemia (including hemolytic and aplastic), thrombocytopenia (including thrombotic thrombocytopenic purpura), leukopenia, agranulocytosis, pancytopenia, and/or other hematologic abnormalities. There may be an increased risk of hypersensitivity reactions in HIV-seropositive patients.[4] The drug should be discontinued immediately at the first sign of a skin rash, jaundice or any other sign of hypersensitivity. Two desensitization regimens have been described: one in a 29-month-old infant[28] and one in a 15-year-old patient with cystic fibrosis.[29]

A hypertensive reaction has been reported in an infant following IV ciprofloxacin 10 mg/kg/day.[30]

Convulsions, increased intracranial pressure, and toxic psychosis have been reported.[2,31–34] Should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). Ciprofloxacin may also cause CNS events including dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts.[2] These reactions may occur following the first dose. Ciprofloxacin should be discontinued and appropriate measures instituted.

Drug interactions: Ciprofloxacin is an inhibitor of CYP1A2.[2] Serious and fatal reactions have been reported in patients receiving concurrent administration of IV ciprofloxacin and theophylline.[2] These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate. Consult appropriate resources for dosing recommendations before combining any drug with ciprofloxacin.

Cisatracurium Besylate

Brand names	Nimbex
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1]
Contraindications and warnings	**Contraindications:** Hypersensitivity to cisatracurium or any of its components.[2] Multiple-dose vials are contraindicated for use in neonates due to the benzyl alcohol preservative.[2] **Warnings:** Use carefully under the supervision of experienced clinicians; personnel should be skilled in airway management, resuscitation, and respiratory support. Intubation and ventilatory support equipment, including oxygen therapy, should be readily available. Reversal agents should be readily available when giving cisatracurium.[2]
Infusion-related cautions	Hypersensitivity reactions, bronchospasm, and laryngospasm have been reported[2,3] but are rare.[2]
Dosage	*Respiratory function must be supported during use of this agent. Concurrent administration of a sedative is also necessary. Monitoring of neuromuscular transmission with a peripheral nerve stimulator is recommended during continuous infusion or with repeated dosing*.[2,4] **Dosing adjustment for obesity:** In morbidly obese women, cisatracurium 0.2 mg/kg of ideal body weight provided good to excellent intubating conditions with a shorter duration of action compared to dosing based on total body weight.[5] **Dosing adjustment for induced hypothermia:** In pediatric patients undergoing mild hypothermia (mean nasopharyngeal temperature 33.7°C) during cardiopulmonary bypass, no dosage reduction was required; however, during moderate hypothermia (mean 24.8°C), a reduction of 60% was required to maintain a constant level of blockade.[6] **Induction and maintenance of neuromuscular blockade** **Continuous infusion:** 1–4 mcg/kg/min.[2,7–10] Clearance is higher in healthy pediatric patients compared to healthy *adult* patients.[2] **Intermittent dosing:** 0.1–0.15 mg/kg administered over 5 seconds followed by 0.03 mg/kg given PRN to maintain pharmacological paralysis.[2,7,10] Onset of action is faster and there is a longer duration of action in infants 1–23 months compared to children 2–12 years of age.[2]
Dosage adjustment in organ dysfunction	No dosage adjustment is required in patients with hepatic or renal dysfunction.[2,11]
Maximum dosage	The maximum dosage has not been established. In a study including 10 neonates and infants after congenital heart surgery, the maximum dose reached in one patient was 11.5 mcg/kg/min.[9] In another study including 19 infants and children receiving cisatracurium, the maximum infusion rate was 10 mcg/kg/min.[10] Response may vary over time, resulting in the need for dosage adjustment.[2] Patients with burns may develop resistance to nondepolarizing neuromuscular blocking agents.[2] The extent of resistance is affected by the size of the burn and time since the burn injury.
Additives	The multiple-dose vials (10 mL) contain benzyl alcohol as a preservative.[2,12] (See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.)

Cisatracurium Besylate

Suitable diluents	D5W, D5NS, NS, D5LR may also be used as a diluent in final concentrations of 0.1–0.2 mg/mL only.[2,12] Do not use LR.[2,12]
Maximum concentration	2 mg/mL for IV push; 0.4 mg/mL for infusion.[2]
Preparation and delivery	Cisatracurium is an acidic solution; do not administer with alkaline solutions.[2,12] May be incompatible with propofol; however, the potential for incompatibility is concentration-dependent and formulation-specific.[12]
IV push	2 mg/mL administered over 5–10 seconds.[2]
Intermittent infusion	Not administered by this method.
Continuous infusion	0.1–0.4 mg/mL.[2,12]
Other routes of administration	IM administration is not recommended due to the potential for tissue irritation.[2] No information available to support administration by other routes.

Comments

Significant adverse effects: Prolonged paralysis has been reported after long-term infusion of neuromuscular blocking agents, including cisatracurium and may be affected by concomitant therapies.[7,13,14] (See Drug Interactions below.) Other factors that potentiate the duration of neuromuscular blockade include acidosis, hyponatremia, hypocalcemia, hypokalemia, and hypermagnesemia.[2,7]

Patients with neurological diseases such as myasthenia gravis may exhibit increased sensitivity. Decreased sensitivity to cisatracurium may occur in patients with severe burns.[2]

Drug interactions: Enflurane and isoflurane anesthesia may potentiate effects of cisatracurium; during long surgical procedures under enflurane and isoflurane anesthesia, up to 30% to 40% reduction in dose may be necessary.[2] Concomitant administration of corticosteroids with neuromuscular blockers is a risk factor for prolonged paralysis.[7] Likewise, concomitant administration with certain antibiotics (e.g., aminoglycosides, clindamycin, and vancomycin) may prolong neuromuscular blockade.[2,7,15] Consult appropriate resources for additional information on drug interactions.

Other: Cisatracurium, in weakening and incompletely paralyzing doses (0.04–0.14 mg/kg/hr [0.7–2.4 mcg/kg/min]) along with intermittent benzodiazepine therapy, has been used to facilitate an isoflurane wean and treat isoflurane withdrawal symptoms in a 4-year-old, critically ill patient.[16]

For neonatal nonemergent intubations, AAP recommends that vagolytic and muscle relaxant agents should be considered and that analgesic agents or anesthetic doses of a hypnotic agent should be administered. Rocuronium or vecuronium is preferred over other available neuromuscular blocking agents.[17]

CISplatin

Brand names	Platinol, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP and USP report that CISplatin has been confused with CARBOplatin; patient harm resulted.[2,3] USP reports that CISplatin has been confused with Cytoxan; no patient harm resulted.[3] ISMP reports that Platinol has been confused with Patanol.[2] USP also reports that Platinol has been confused with Plaquenil; no patient harm resulted.[3]
Contraindications and warnings	**U.S. boxed warning:** CISplatin should be administered under the supervision of a qualified physician. Use caution to prevent inadvertent overdose. (See Maximum Dosage section.) CISplatin is associated with severe renal toxicity. Also associated with other serious dose-related toxicities such as myelosuppression, nausea, and vomiting. CISplatin can cause ototoxicity that is more pronounced in children. CISplatin has been associated with serious anaphylactic-like reactions.[4,5] (See Infusion-Related Cautions section.) **Contraindications:** CISplatin should not be used in patients with preexisting renal impairment, myelosuppression, or hearing impairment. Should also not be used in patients with known history of hypersensitivity to CISplatin or any components.[4,5] **Other warnings:** Occasionally, fatal dosing errors have occurred when CISplatin has been inadvertently substituted for carboplatin. Can cause serious acute leukemia and neuropathies.[4,5]
Infusion-related cautions	Anaphylactic-like reactions, including facial edema, bronchoconstriction, tachycardia, and hypotension, may occur within minutes of administration. Epinephrine, corticosteroids, and antihistamines have been used.[4] Because extravasation may cause tissue sloughing and necrosis, the infusion should be stopped if the patient complains of discomfort.[5,6] If extravasation occurs, attempt to remove any residual drug from tissues. Because of extravasation and infiltration risk, small veins in the dorsum of the hand or foot and scalp veins should be avoided if at all possible. Severity of tissue damage appears to occur more often when concentration of solution is >0.5 mg/mL.[5] (See Appendix E for additional information regarding extravasation treatment.)
Dosage	Consult individual protocol for complete dosing information. CISplatin should be administered with a regimen of hydration with or without mannitol and/or furosemide. (See Comments section.) Should not be given to patients with pre-existing renal or hearing impairment or myelosuppression. *Verify any dose exceeding 100 mg/m^2 per cycle, to prevent possible overdose.* **The following dosing regimens have been used in pediatric patients:** **Intermittent dosing:** 37–75 mg/m^2 q 2–3 wk or 50–100 mg/m^2 q 3–4 wk.[4,5] **Daily dosing:** 15–20 mg/m^2/day for 5 days q 3–4 wk.[4,5,14,15] **Bone marrow/stem cell transplantation:** 55 mg/m^2/day for 72 hours by continuous infusion (165 mg/m^2).[4,5] **Brain tumor (recurrent):** 60 mg/m^2/day for 2 days q 3–4 wk.[4,5,7]

Dosage *(cont.)*	**Neuroblastoma:** 60–100 mg/m^2 once q 3–4 wk[4,8,9] or 30 mg/m^2 every week.[4,5] **Osteogenic sarcoma:** 60–100 mg/m^2 once q 3–4 wk[4,5,10–13] or 30 mg/m^2 every week.[4,5] A repeat course should not be given until the patient's renal, hematologic, and otic functions are within acceptable limits.[4]
Dosage adjustment in organ dysfunction	The manufacturer states that CISplatin is contraindicated in patients with pre-existing renal dysfunction.[4] Another reference recommends that if CrCl is 10–50 mL/min, administer 75% of the normal dose and if CrCl is <10 mL/min, administer 50% of the normal dose.[16] The manufacturer also recommends that repeat dosages be held until SCr <1.5 mg/dL, WBC count ≥4000/mm^3, platelets ≥100,000/mm^3, and BUN <25.[4] Decrease dosage in infants <6 months of age due to decreased renal tubular secretion and decreased renal function.[5]
Maximum dosage	It is important to differentiate between daily doses and total dose per cycle or course of treatment. Verify any CISplatin dose exceeding 100 mg/m^2 per course.[4] Doses >100 mg/m^2 per course q 3–4 wk are rarely used.[4]
Additives	None.
Suitable diluents	D5¼NS, D5½NS, D5NS, ¼NS, ⅓NS, ½NS, NS.[5,17]
Maximum concentration	Not established.
Preparation and delivery	**Preparation:** Skin reactions may occur following exposure; therefore, wear gloves when preparing and administering.[4] If exposure occurs, wash area with soap and water. Needles, syringes, catheters, or IV administration sets that contain aluminum parts that may come in contact with CISplatin should not be used for preparation or administration of the drug, because this may result in precipitate formation.[4,17] **Stability:** Do not infuse in solutions containing <¼NS; stable when combined with mannitol (12.5–50 g mannitol/L).[5] **Compatibility:** Incompatible with sodium bicarbonate and variable stability in D5W.[17] For PN compatibility information, please see Appendix D.
IV push	Although rapid administration over 1–5 minutes has been used, it is associated with an increased risk of ototoxicity and nephrotoxicity.[5]
Intermittent infusion	Concentration not specified. Diluted in compatible fluid, it has been given over 15–20 minutes without adverse effects.[5,7–15]
Continuous infusion	The manufacturer recommends diluting the dose in 2 L of D5W and sodium containing fluid (see Suitable Diluents section) with 18.75 g mannitol/L and infusing over 6–8 hours.[4,5,17] Other studies have reported stability at concentrations of 20, 50, 200, and 500 mg/L.[17] Although CISplatin has been infused over 6–8 hours, 8–12 hours, or as a 24-hour infusion in order to decrease nephrotoxicity,[5] these various rates of administration have generally not been associated with a reduction in renal toxicity.[5]

CISplatin

Other routes of administration	Not administered IM.

Comments

Significant adverse effects: Aggressive hydration should be given to ensure good urinary output and reduce the likelihood of nephrotoxicity associated with CISplatin.[19] Several protocols have been advocated. One regimen consists of administration of 1–2 L of an NS-containing fluid over 8–12 hours before CISplatin.[17] The manufacturer recommends diluting the dose in 2 L of compatible fluid containing 37.5 mg of mannitol (18.75 g/L) and infusing over 6–8 hours.[4] Others have given infusion over 15–120 minutes and by continuous infusion over 1–5 days.[17]

Nephrotoxicity, neurotoxicity, and ototoxicity increase with cumulative doses.[18–26] Renal toxicity has been noted in 28% to 36% of patients treated with a single 50 mg/m^2/dose.[4]

Ototoxicity (high-frequency hearing loss) is especially pronounced in children and is related to a cumulative CISplatin dose >200 mg/m^2.[5] Variants in the thiopurine S-methyltransferase (TPMT) gene are associated with increased risk of ototoxicity in children receiving CISplatin. An audiometric test should be performed before therapy is initiated and prior to each subsequent dose of medication.[4]

Neurotoxicity, typically as peripheral neuropathies, have been reported, usually after prolonged therapy but may occur after a single dose. Symptoms may begin during treatment or 3–8 weeks after the last dose of CISplatin. Neuropathies may progress even after discontinuation of CISplatin and may be irreversible in some patients.[4]

CISplatin is associated with a high (>90%) risk of emesis.[27] Patients should receive antiemetic therapy to prevent acute and delayed nausea and vomiting. The recommended therapy is a 5HT3 receptor antagonist in combination with dexamethasone on every day chemotherapy is administered.[27,28] These agents may be continued for up to 4 days after chemotherapy administration for the prevention of delayed nausea and vomiting. Breakthrough medications should also be offered, such as a phenothiazine (e.g., prochlorperazine), a butyrophenone (e.g., droperidol), a substituted benzamide (e.g., metoclopramide), or a benzodiazepine (e.g., lorazepam).[28]

Monitoring: Monitor renal function (e.g., SCr, BUN, CrCl), electrolytes (e.g., magnesium, calcium, and potassium), audiography, neurological tests, liver function tests, CBC with platelets, and urinalysis.[4,5] Electrolyte supplementation may be necessary.[4]

Drug interactions: Use caution with concomitant aminoglycoside use due to increased risk of nephrotoxicity and ototoxicity.[4]

Clindamycin Phosphate

Brand names

Cleocin

Medication error potential

Look-alike, sound-alike drug names.

USP reports that clindamycin phosphate has been confused with clarithromycin, Clinoril, vancomycin, and gentamicin. Confusion has also been noted between Cleocin and Cipro, Claforan, Cubicin, and oxycodone and acetaminophen.[1]

Contraindications and warnings

U.S. boxed warning: Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] Cleocin phosphate is highly associated with severe CDAD infections and should be reserved for the treatment of more severe infections. If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]

Contraindications: Contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin.[2]

Other warnings: Clindamycin does not adequately penetrate into the cerebrospinal fluid and should not be used to treat meningitis.[2]

Infusion-related cautions

If a decision is made to give this medication to a patient with known clindamycin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, IV steroids, and antihistamines.[2]

Thrombophlebitis and pain may occur with infusion.[2]

Dosage

Neonates

Dose is based on postnatal age (PNA) and weight or postmenstrual age and PNA.

PNA	<1200 g	1200–2000 g	>2000 g
<7 days	10 mg/kg/day divided q 12 hr[3]*	10 mg/kg/day divided q 12 hr[3]	15 mg/kg/day divided q 8 hr[3]
≥7 days		15 mg/kg/day divided q 8 hr[3]*	20–30 mg/kg/day divided q 6–8 hr[3–5]

*Until 4 weeks of age.

Infants and children

Pediatric patients >16 years may receive the usual *adult* dose (600–1200 mg/day divided q 6–12 hr).[2]

Mild-to-moderate infection: 15–25 mg/kg/day (350 mg/m^2/day) divided q 6–8 hr.[2,3]

Severe infection: 25–40 mg/kg/day (450 mg/m^2/day) divided q 6–8 hr.[2,3,6–8]

Bacterial endocarditis (prophylaxis)

Dental, oral, respiratory tract, or esophageal procedures*: Single 20 mg/kg/dose (up to 600 mg) given as single dose 30–60 minutes before a procedure.[9] Only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome. (See Other in the Comments section.)

**Procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.*[9]

Surgical (colorectal, appendectomy, incision through the oral mucosa, ruptured viscus): 10 mg/kg/dose preoperative recommended.[3]

Clindamycin Phosphate

Dosage adjustment in organ dysfunction	No dose adjustment for renal dysfunction.[10] Although the half-life is prolonged in hepatic dysfunction no specific dosage adjustment is recommended.[2]
Maximum dosage	Not to exceed 4.8 g/day in *adults,*[2] not to exceed 1200 mg in a single, 1-hour infusion.[2] 600 mg IM is the maximum dose.[2]
Additives	9.45 mg/mL benzyl alcohol.[2,11] (See Appendix C for specific information about benzyl alcohol and potential for toxicity.)
Suitable diluents	NS, LR, D5W, D10W, D5NS, D5R, D5½NS.[11] Stability varies depending on the concentration, diluents, and storage conditions. See appropriate resource.
Maximum concentration	18 mg/mL.[2,11]
Preparation and delivery	**Delivery system issues:** Premade IV preparations are in special plastic containers that can leach out very small amounts of chemicals when in contact with solutions. Toxicity from the leached chemicals has not been evaluated in pediatrics.[2,12] **Stability:** Do not refrigerate because crystallization may occur.[11] Bulk package preparations should not be directly infused and should be prepared with single entry use. Discard any unused portion within 24 hours after initial entry.[11] **Compatibility:** See Appendix D for PN compatibility information.[13]
IV push	Not recommended.[2,11] Hypotension and cardiopulmonary arrest may occur following rapid IV administration.[2,14]
Intermittent infusion	Infuse over 10–60 minutes, not to exceed a rate of 1800 mg/hr.[2,11]
Continuous infusion	Has been reported in *adults* at normal daily doses infused over 24 hours without a specified concentration.[15] 0.75–1.25 mg/min has been given.[2,11]
Other routes of administration	IM not to exceed 600 mg.[2,11] Pain induration and sterile abscess may occur with IM injections.[2]
Comments	**Rare adverse events:** Rare cases of erythema multiforme, resembling Stevens-Johnson syndrome, and anaphylactoid reactions have been reported in *adults.*[2] Leukopenia and eosinophilia have been reported.[2] **Monitoring:** IV clindamycin or vancomycin are recommended for treatment of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). In addition to minimum inhibitory concentration testing, a D-test should be performed by the clinical laboratory. A negative D-test suggests that resistance to clindamycin will not develop during therapy; hence, the patient can be managed with clindamycin.[16] During prolonged therapy periodic liver and kidney function tests and blood counts should be performed. **Drug interactions:** Clindamycin has been reported to aggravate neuromuscular disease and induce neuromuscular blockade.[17,18] Clindamycin may antagonize the activity of erythromycin and should not be used concurrently.[2]

Clindamycin Phosphate

Comments *(cont.)*

Other: Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable: (1) prosthetic cardiac valve or prosthetic material used for cardiac valve repair; (2) previous infective endocarditis; (3) congenital heart disease (CHD) in a person with a) unrepaired cyanotic CHD, including palliative shunts and conduits, b) completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure, c) repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization); and (4) cardiac transplantation recipients who develop cardiac valvulopathy.[9]

Biochemical warfare or bioterrorism: The CDC and other experts recommend treatment of inhalational anthrax spores due to biologic warfare or bioterrorism should be started on a multiple-drug parenteral regimen that may include clindamycin.[19,20]

Co-Trimoxazole (Trimethoprim–Sulfamethoxazole)

Brand names	Generic
Medication error potential	USP reports that co-trimoxazole (trimethoprim–sulfamethoxazole) has been confused with sulfasalazine. USP also reports confusion of trimethoprim with triamterene and trimethobenzamide.[1]
Contraindications and warnings	**Contraindications:** In those (1) with known hypersensitivity to sulfa drug, trimethoprim, or any component of the formulation; (2) with documented megaloblastic anemia due to folate deficiency; (3) <2 months of age*; (4) who are pregnant or breast-feeding since sulfonamides are excreted in the milk and may cause kernicterus in the infant; and (5) with a history of immune thrombocytopenia with sulfonamide use.[2] **Except for* Pneumocystis carinii *prophylaxis in infants >4 weeks old who were born to HIV-infected mothers.*[3] **Warnings:** Fatalities have occurred due to severe dermatologic reactions (i.e., Stevens-Johnson syndrome and toxic epidermal necrolysis). Sulfonamides should be discontinued at the first appearance of skin rash.[2] Fulminant hepatic necrosis and a variety of blood dyscrasias (e.g., agranulocytosis, aplastic anemia) have been reported.[2] Dose-dependent hemolysis may occur in patients with G6PD-deficiency.[2] (See Rare Adverse Effects in the Comments Section.) Use caution in use in patients at risk for folate deficiency.[2] Cough, shortness of breath, and pulmonary infiltrates are hypersensitivity reactions of the respiratory tract that have been reported.[2] Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	Pain, local irritation, inflammation, and rarely thrombophlebitis may occur.[2]
Dosage	Dosage is based on trimethoprim component. **Neonates:** Not recommended for those <2 months of age since sulfonamides may cause kernicterus by displacing bilirubin from plasma protein-binding sites[2]; however, may be used for *Pneumocystis carinii* prophylaxis in infants born to HIV-infected mothers.[3] **Infants and children** **Severe infections:** 8–12 mg/kg/day divided q 6–12 hr.[2,3] Give up to 14 days for severe urinary tract infection and 5 days for shigellosis.[2] **Meningitis (not first-line; alternative therapy for *Listeria monocytogenes*):** 15–20 mg/kg/day divided q 6–12 hr.[4–7] ***Pneumocystis carinii* pneumonia:** 15–20 mg/kg/day divided q 6–8 hr[3] for 14–21 days.[2,3,8,9]
Dosage adjustment in organ dysfunction	If CrCl is 15–30 mL/min, the manufacturer recommends to give 50% the normal dose.[2] Not recommended by the manufacturer if CrCl is <15 mL/min.[2] Another reference states if GFR ≥30 give normal dose; if GFR 10–29, give 5–10 mg/kg q 8 hr; not recommended if GRF <10, but if required give 5–10 mg/kg q 24 hr.[10]

Co-Trimoxazole (Trimethoprim–Sulfamethoxazole)

Maximum dosage	20 mg/kg/day for *Pneumocystis carinii* pneumonia[2,11,12]
Additives	Contains sodium metabisulfite, 400 mg/mL propylene glycol and 1% benzyl alcohol.[2,13] (See Appendix C for specific information about sulfite hypersensitivity, benzyl alcohol, and propylene glycol toxicity.)
Suitable diluents	D5W.[2,13]
Maximum concentration	5 mL of the concentrate in 125 mL of D5W,[2,13] or 5 mL of concentrate in 75 mL of D5W in fluid-restricted patients.[2,13]
Preparation and delivery	**Stability:** Do not refrigerate concentrate for injection.[2,13] Stability at room temperature is 5 mL concentrate in 125 mL D5W is stable for 6 hours[2,13]; 5 mL concentrate in 100 mL D5W is stable for 4 hours[2,13]; 5 mL concentrate in 75 mL D5W is stable for 2 hours.[2,13] **Compatibility:** See Appendix D for PN compatibility information.[14]
IV push	Not recommended.[2,13]
Intermittent infusion	Over 60–90 minutes.[2,13]
Continuous infusion	Not used.
Other routes of administration	None.
Comments	**Significant adverse effects:** Stevens-Johnson syndrome and toxic epidermal necrolysis may occur with sulfonamide therapy.[2] One to three days before the appearance of a rash, patients develop a prodrome of fever, stinging eyes, and sore throat.[15] The initial lesions are erythematous to purpuric macules, which first appear on the trunk and spreading to the face and proximal extremities.[15] Lesions may then progress to full-thickness necrosis with flaccid blisters. Most patients (90%) develop buccal, oral, and genital mucosal involvement with erythema and erosions.[15] Sulfonamide should be discontinued immediately at first sign of rash.[2] Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, and eosinophilia have been reported.[2] Hemolysis has been reported in individuals with G6PD deficiency.[2] Hepatitis, including cholestatic jaundice, hepatic necrosis, and liver failure, one of which required transplantation.[2,16,17] **Rare adverse effects:** Trimethoprim can cause hyperkalemia.[2] This can occur with both large and standard dosages of trimethoprim but generally occurs in those with renal impairment, hypoaldosteronism, or concurrent medications known to impair renal potassium excretion.[18] Management frequently requires discontinuation of trimethoprim, volume repletion with isotonic fluids, and administration of therapies specific to hyperkalemia. **Monitoring:** Serum potassium, serum transaminases, and bilirubin. Coagulation time should be monitored in those on warfarin.

Co-Trimoxazole (Trimethoprim–Sulfamethoxazole)

Comments *(cont.)*

Drug interactions: Trimethoprim is 45% and sulfamethoxazole is 70% bound to plasma protein.[2] Because co-trimoxazole is associated with numerous drug interactions, consult appropriate resources for dosing recommendations before combining any drug with co-trimoxazole.

Laboratory interference: The presence of trimethoprim and sulfamethoxazole may interfere with the Jaffe assay for creatinine, resulting in about 10% overestimation.[2] The trimethoprim component can interfere with determination of serum methotrexate concentrations.[2] This occurs if a bacterial dihydrofolate reductase is used as the binding protein source in the competitive binding protein technique but does not occur if a radioimmunoassay is used.[2]

Coagulation Factor VIIa (Recombinant) (rFVIIa)

Brand names	NovoSeven RT
Medication error potential	None noted.
Contraindications and warnings	**Warnings:** Use caution when administering to individuals with known hypersensitivity to NovoSeven, its components, or who have hypersensitivity reactions to mouse, hamster, or bovine proteins.[1] Use caution when administering rFVIIa to patients with increased risk of thromboembolic complications, such as liver disease, sepsis, crush injury, coronary heart disease, disseminated intravascular coagulation, postoperative immobilization and neonates.[1] Use of rFVIIa in patients outside of labeled indications may be associated with an increased risk for development of thrombosis.[1,2]
Infusion-related cautions	Thrombophlebitis occurred during continuous infusion via peripheral vein.[3] (See Preparation and Delivery section and Continuous Infusion section.)
Dosage	**Hemophilia A or B with inhibitors to Factor VIII or IX[1]** **Prophylaxis for invasive procedures:** 90 mcg/kg prior to surgery with doses repeated at 2-hour intervals during the procedure. **Minor procedures postoperatively:** 90 mcg/kg q 2 hr for 48 hours followed by q 2–6 hr until healing. **Major procedures postoperatively:** 90 mcg/kg q 2 hr for 5 days after surgery followed by q 4 hr intervals until healing. Alternatively, continuous infusion with Factor VII concentration monitoring (target concentration 10 International Units/mL) to determine maintenance infusion rate has been used.[3] Others report infusing 50 mcg/kg/hr for 5 days then 25 mcg/kg/hr for 5 days.[4] **Treatment:** 90 mcg/kg (35–120 mcg/kg) q 2 hr until hemostasis occurs or treatment is felt to be ineffective. The dosing interval may be adjusted according to bleeding severity. Also, continuous infusion has been used.[5] For severe bleeds, continue dosing q 3–6 hr to maintain hemostatic plug.[1] Doses of 250–300 mcg/kg have been used successfully in joint or muscle spontaneous bleeds with a median number of 3 doses required.[6] **Congenital Factor VII deficiency (prophylaxis for invasive procedures):** 15–30 mcg/kg q 4–6 hr until hemostasis.[1,7] Doses as low as 10 mcg/kg have been effective.[1] **Acquired hemophilia treatment:** 70–90 mcg/kg q 2–3 hr until hemostasis occurs.[1] **Surgery-related bleeding** **Cardiac surgery with cardiopulmonary bypass (CPB):** Eight children 5 days to 8 years of age received 30 or 60 mcg/kg repeated in 15 minutes and again in 2 hours if bleeding continued.[8] A single dose of 70 mcg/kg was effective in a 4-month-old with bleeding after atrial septal defect repair.[9] A 9-month-old received 2 doses of 90 mcg/kg for intraoperative bleeding.[10] On the other hand, a randomized, double-blind, placebo controlled trial found no benefit, and time to chest closure was prolonged in 42 infants receiving rFVIIa compared to 40 infants receiving standard treatment.[11] **Bleeding during extracorporeal membrane oxygenation (ECMO):** An 11-year-old and a 13-year-old were given 90 mcg/kg q 4 hr for 3 doses or q 2 hr for 10 doses to control bleeding.[12] Four children from age 6 days to 33 months were given 2 doses of 90–120 mcg/kg 4 hours apart.[13] All except the 13-year-old were on ECMO after open heart surgery. Of interest, an infant who failed to be weaned from CPB after a Ross procedure for aortic stenosis was placed on ECMO and developed thrombotic occlusions of both subclavian arteries and truncus brachiocephalicus after receiving rFVIIa for uncontrollable bleeding.[14]

Coagulation Factor VIIa (Recombinant) (rFVIIa)

Dosage *(cont.)*

Miscellaneous bleeding: Four days after cardiac surgery, a 10-month-old male with Noonan syndrome developed GI bleeding unresponsive to standard treatment.[15] He initially responded to a dose of 90 mcg/kg but began bleeding again after about 8 hours. Two more doses were given and the bleeding stopped. Another 16-month-old being treated for acute megakaryoblastic leukemia developed severe GI bleeding that responded to 100 mcg/kg given at 0, 2, and 12 hours.[16]

Liver failure coagulopathy

Bleeding management: Twenty-two children with liver disease received doses ranging from 36–118 mcg/kg to treat a variety of bleeding episodes.[17,18] A 3-month-old, a 9-year-old, and an 11-year-old received 67 mcg/kg × 3, 130 mcg/kg × 2, and 200 mcg/kg to control bleeding from various sources.[19] Following a right hepatectomy, a 5-month-old boy with internal bleeding was given a single dose of 90 mcg/kg.[20]

Prior to invasive procedure: Six children (2 months to 15 years) received doses of 34–163 mcg/kg prior to liver biopsy and other invasive procedures.[18]

Transplant: A 2½-year-old and a 7-year-old received 100 mcg/kg prior to transplant, and one of them received a second dose 2 hours later during transplant.[21] A 7-month-old with an international normalized ratio of 3 and multiple bleeding sites received 300 mcg/kg prior to transplant.[22] Seven children with bleeding after liver graft reperfusion received 37–168 mcg/kg that resulted in improved hemostasis.[22] No postoperative thrombotic events were noted in these children. On the other hand, four *adults* undergoing liver transplantation received 90 mcg/kg preoperatively and intraoperatively. One developed portal vein thrombosis and another myocardial ischemia leading the authors to express concern over the potential for thrombotic complications.[23]

Congenital platelet disorders: A 15-year-old girl with Bernard-Soulier syndrome received 98 mcg/kg × 2 that controlled severe menorrhagia. On a separate occasion, she received 2 doses of 98 and 122.5 mcg/kg that controlled severe epistaxis and mild menorrhagia.[24] Four children with Glanzmann thrombasthenia received 89–116 mcg/kg q 2 hr until bleeding stopped.[25] Thirty-three uses of rFVIIa (100 mcg/kg q 90 min × 3 doses) were evaluated in seven children with Bernard-Soulier syndrome or Glanzmann thrombasthenia.[26] When rFVIIa was started 30–45 minutes prior to a planned surgical intervention (seven procedures in five children), no bleeding occurred postoperatively; however, efficacy in treating an established bleed was variable.

Preterm neonates

Intraventricular hemorrhage (IVH): The incidence of IVH was not different in 10 infants who received rVIIa compared to those who did not, and the two with umbilical artery catheters developed thrombi at the catheter tip.[27] Another neonate with IVH was given rVIIa, and while the bleeding stopped, the infant did not survive the grade IV bleed.[28]

Necrotizing enterocolitis (NEC): During surgical management of NEC, four very low birth weight infants with intraoperative bleeding received rVIIa.[29] Bleeding was controlled in three of the four; however, one infant developed a brachial artery thrombus necessitating thrombectomy and arterial reconstruction, and another had transient ischemia of the distal phalanges.

Pulmonary hemorrhage: Four very low birth weight infants were treated for 2 or 3 days.[28,30,31] After treatment, all had stabilization of coagulation parameters. However, one developed pulmonary hemorrhage 8 hours after the dose.[28]

Dosage adjustment in organ dysfunction

Not reported.

Maximum dosage

Not established. Accidental overdoses of 246–986 mcg/kg have been reported without thrombotic complications.[1] Antibodies against rFVIIa were detected in a newborn with congenital Factor VII deficiency who received 800 mcg/kg rFVIIa.[1]

Coagulation Factor VIIa (Recombinant) (rFVIIa)

Additives	Contains polysorbate 80, mannitol, and sucrose.[1]
Suitable diluents	Histidine diluent (provided with lyophilized powder).[1]
Maximum concentration	1000 mcg/mL (reconstituted).[1]
Preparation and delivery	Bring to room temperature prior to reconstitution. Reconstitute with provided diluent. Reconstituted solution must be administered within 3 hours.[1] **Compatibility:** The addition of heparin to reduce thrombophlebitis results in a 20% to 30% loss of activity unless the pH is adjusted from 5.5 to 7.4.[3]
IV push	Over 2–5 minutes.[1]
Intermittent infusion	Not indicated.
Continuous infusion	A parallel infusion of saline (20 mL/hr in *adults*) into same vein as undiluted rFVIIa may minimize the thrombophlebitis.[5] Selection of infusion pump devices appeared to be important to the success of continuous infusion.[5]
Other routes of administration	Not indicated.
Comments	**Pharmacokinetics:** Children have a shorter half-life, more rapid clearance, and larger volume of distribution at steady state than *adults*.[32] **Monitoring:** Factor VII deficient patients should be monitored for Factor VII coagulant activity and prothrombin time (PT) before and after administration. Antibody formation should be suspected if Factor VIIa activity fails to reach expected level, PT is not corrected or bleeding is not controlled after treatment with recommended doses.[1] All patients receiving rFVIIa should be monitored for signs and symptoms of activiation of the coagulation system or thrombosis.[1]

Conivaptan

Brand names	Vaprisol
Medication error potential	None reported by ISMP or USP.[1–3]
Contraindications and warnings	**Contraindications:** Hypersensitivity to any component, allergy to corn or corn products (due to dextrose component), hypovolemic hyponatremia, anuria, and concomitant administration of medications that are potent CYP3A4 inhibitors.[4–7] (See Drug Interactions in the Comments section.) **Warnings:** Conivaptan is not indicated for treatment of congestive heart failure and should only be used for treatment of hyponatremia in patients with heart failure when the benefit of raising serum sodium outweighs the risk of adverse effects.[4,5,7] Avoid rapid correction of serum sodium (>12 mEq/L in 24 hours) due to the risk of osmotic demyelination syndrome. Discontinue therapy if the patient develops a rapid rise in serum sodium. If hyponatremia persists, conivaptan may be resumed at a lower dose if there is no evidence of neurologic sequelae from rapid rise in sodium.[4,5]
Infusion-related cautions	Conivaptan has been associated with infusion site reactions, potentially due to propylene glycol, which was an additive in the previously-marketed formulations available in ampules.[4,6] The premixed conivaptan in D5W solutions do not contain propylene glycol.[4] Administer via large veins and rotate infusion site every 24 hours to minimize risk of irritation.[4] (See Appendix E for information regarding infiltration.)
Dosage	Conivaptan has not been extensively studied in pediatric patients. Currently there is no established dosage range for pediatric patients. One report describes conivaptan use for aggressive hydration to prevent tumor lysis syndrome in a 13-year-old with lymphoma and syndrome of inappropriate antidiuretic hormone (SIADH) as follows[8]: **Loading dose:** 10 mg IV infused over 30 minutes. **Maintenance dose:** 10 mg/day infused over 24 hours titrated up to 30 mg/day infused over 24 hours. This treatment regimen was successful and the patient experienced no adverse effects.[8] The following doses are recommended in *adults*[4–6]: **Loading dose:** 20 mg IV infused over 30 minutes. **Maintenance dose:** 20–40 mg/day via continuous infusion over 24 hours (0.83–1.7 mg/hr). Alternatively, one *adult* randomized, placebo-controlled trial reported that intermittent 30-minute infusions of 20 mg once or twice daily were effective in increasing serum sodium compared to placebo.[9]
Dosage adjustment in organ dysfunction	Increased systemic exposure in patients with hepatic impairment, and increased AUC in patients with renal impairment has occurred following administration of *oral* conivaptan.[4] Use caution when administering to patients with hepatic or renal impairment. A 50% dosage reduction is recommended in *adults* with moderate hepatic impairment (Child-Pugh Class A-C) or moderate renal impairment (CrCl 30–60 mL/min): loading dose of 10 mg followed by continuous infusion of 10 mg/day, with the option to titrate up to 20 mg/day if serum sodium does not rise at the desired rate. In patients with CrCl <30 mL/min, conivaptan is not recommended.[4]

Conivaptan

Maximum dosage	In *adults*, after giving loading dose, do not exceed 40 mg/day for 4 days of therapy.[4,5]
Additives	None noted.[4]
Suitable diluents	D5W.[4,5]
Maximum concentration	0.2 mg/mL.[4,5]
Preparation and delivery	Conivaptan is available as a premixed solution in D5W (20 mg/100 mL).[4,5] Conivaptan may be administered concomitantly via Y-site with NS but not with LR.[4]
IV push	Not indicated.
Intermittent infusion	Loading dose is given over 30 minutes.[4–6] Maintenance doses are recommended to be administered by continuous infusion; however, intermittent 30-minute maintenance infusions of 20 mg once or twice daily have been studied in *adults*.[9]
Continuous infusion	The manufacturer recommends that maintenance doses are to be administered via continuous infusion.[4,5]
Other routes of administration	No information to support administration by other routes.[4]
Comments	**Monitoring:** Serum sodium, vital signs, and neurologic and fluid statuses.[4–6] **Drug interactions:** Conivaptan is a substrate for CYP3A4 and is also a potent inhibitor of CYP3A4. Concomitant use with potent CYP3A4 inhibitors is contraindicated and caution should be used if co-administering drugs that are substrates for CYP3A4.[4–6] Subsequent treatment with CYP3A4 substrates should not be initiated until >1 week after the last conivaptan infusion.[4] Consult appropriate resources for dosing recommendations before combining any drug with conivaptan. **Pharmacokinetic considerations:** Nonlinear metabolism likely due to inhibition of its own metabolism.[4,6] **Pharmacodynamic considerations:** Net result is increased free water excretion.[4]

Cyclophosphamide

Brand names	Cytoxan, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that cyclophosphamide has been confused with cyclosporine; no patient harm resulted.[2] USP reports that Cytoxan has been confused with cisplatin and Cytarabine; no patient harm resulted. USP also reports that Cytoxan has been confused with Cytosar-U; patient harm resulted.[2]
Contraindications and warnings	**Contraindications:** Cyclophosphamide is contraindicated in patients with known hypersensitivity to the drug and patients with severely depressed bone marrow.[3] **Warnings:** Secondary malignancies, hemorrhagic cystitis, and acute cardiac toxicity have developed (see Comments section). Cyclophosphamide also carries an increased risk of infection.[3]
Infusion-related cautions	Anaphylaxis, including fatal hypersensitivity reactions, has occurred.[3]
Dosage	Consult individual protocol for complete dosing information. Cyclophosphamide is used as a component of combination therapy to treat both oncologic and nononcologic diseases. Specifically, the FDA approves it for the oncologic treatment of lymphomas, Hodgkin disease, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, ovarian adenocarcinoma, retinoblastoma, and breast cancer.[3] Nononcologic FDA indications include pediatric minimal change nephrotic syndrome.[3] It may also be used in systemic lupus erythematosus (SLE), rheumatoid arthritis, vasculitis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, antibody-induced pure red cell aplasia, and in consolidation therapy prior to autologous bone marrow transplant (BMT). Selected dosage regimens include the following: **Pediatric solid tumors** **Induction:** 40–50 mg/kg IV (1.5–1.8 g/m^2) in divided doses over 2–5 days.[3,4] **Maintenance:** 10–15 mg/kg (350–550 mg/m^2) given q 7–10 days or 3–5 mg/kg (110–185 mg/m^2) twice weekly.[3–5] **SLE:** 500–750 mg/m^2 every month (maximum dose 1 g/m^2).[4,6] Continuous daily doses of 60–120 mg/m^2 (1–2.5 mg/kg) have been given every day.[4,7] **BMT-conditioning regimen:** 50 mg/kg IV once daily for 3–4 days.[4,8] **Juvenile idiopathic arthritis/vasculitis:** 10 mg/kg IV q 2 wk.[4]
Dosage adjustment in organ dysfunction	If CrCl is <10 mL/min, administer 75% of the usual dosage.[3,4,9]
Maximum dosage	Not established.
Additives	None.

Cyclophosphamide

Suitable diluents	D5W, D5NS, D5R, LR, NS, ½NS, sodium lactate injection ⅙M.[3,10]
Maximum concentration	20–25 mg/mL.[3,4,10]
Preparation and delivery	**Preparation:** Reconstitute cyclophosphamide with NS. May also use SW; however, cyclophosphamide reconstituted with SW is hypotonic and should not be administered by direct IV injection; dilute with suitable diluents prior to IV administration.[3,10] Gently swirl vial after adding diluents to dissolve all the powder; allow vial to stand for a few minutes if powder still apparent.[3] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Dilute with NS for direct injection/IV push.[3]
Intermittent infusion	Most infusions occur over 30–60 minutes.[4] If the dosage is >1800 mg/m^2, the infusion should last 4–6 hours.
Continuous infusion	Although cyclophosphamide may be administered continuously,[4,8,10] its use is not established.
Other routes of administration	Cyclophosphamide has been administered IM,[10] but use is not established. IM administration may be less effective as this route bypasses the liver.[4] May also be given intraperitoneally or intrapleurally.[10] Reconstitute with NS if administering via IM, IP, or intrapleural route.[3]
Comments	**Significant adverse effects:** Cyclophosphamide is associated with hemorrhagic cystitis.[3] Patients should be encouraged to drink excess fluids and void frequently starting 24 hours before therapy and continuing 24 hours after therapy.[3,4] Mesna therapy should be used with high dosages of cyclophosphamide (i.e., dosages >1 g/m^2/day).[3] The urine should be examined for the presence of RBCs, an indicator of hemorrhagic cystitis. Cyclophosphamide is associated with long-term gonadal function damage and infertility in pediatric patients.[3,4] Cyclophosphamide is associated with a high (>90%) risk of emesis in IV dosages >1500 mg/m^2 and a moderate (30% to 90%) risk of emesis with IV dosages ≤1500 mg/m^2.[11] Patients should receive antiemetic therapy to prevent acute and delayed nausea and vomiting. The recommended therapy is a 5HT3 receptor antagonist in combination with dexamethasone on each day chemotherapy is administered.[11,12] These agents may be continued for up to 4 days after chemotherapy administration for the prevention of delayed nausea and vomiting. Breakthrough medications should also be offered. **Rare adverse effects:** Cardiac toxicity has been reported at dosages ranging from 2.4–26 g/m^2.[3] **Monitoring:** Urine output, electrolytes, BUN, SCr, CBC with differential and platelets, urine specific gravity, and urinalysis.[3,4] **Drug interactions:** Cyclophosphamide is a major substrate for CYP2B6 and 3A4 and a minor substrate for CYP2A6, 2C9, and 2C19; it is associated with numerous drug interactions. Consult appropriate resources for dosing recommendations before combining any drug with cyclophosphamide.[3,4] Concomitant allopurinol use may enhance toxicity, particularly bone marrow suppression.[3,4]

CycloSPORINE

Brand names	Sandimmune
Medication error potential	Look-alike, sound-alike drug names. USP reports that Sandimmune has been confused with Sandostatin. CycloSPORINE has been confused with cyclophosphamide and has potential for confusion with cephalexin.[1] ISMP reports that cycloSPORINE has been confused with cycloserine and Sandimmune has been confused with Sandostatin[2]
Contraindications and warnings	**U.S. boxed warning:** CycloSPORINE should only be prescribed by physicians with experience in immunosuppressive therapies. Patients undergoing immunosuppressive therapies are at increased risk for infection and the development of lymphoma. (See product literature for complete information.) **Contraindications:** Patients with hypersensitivity to cycloSPORINE or Cremophor EL.[3] (See Comments section.) **Other warnings:** Anaphylactic reactions have occurred.[3] In phase I/II trials of high-dose cycloSPORINE for multidrug-resistant tumors in 21 children, anaphylactoid reactions occurred in five patients due to improper mixing of the Cremophor EL vehicle.[4] With high-dose cycloSPORINE, it was recommended that a homogenous mixture be achieved and premedication with antihistamine and corticosteroid be administered.[4,5] Anaphylaxis requires immediate discontinuation of the infusion and emergency treatment with epinephrine and oxygen.[3]
Infusion-related cautions	Patients should be under continuous observation for signs of hypersensitivity reaction during the first 30 minutes of the infusion and frequently thereafter.[3]
Dosage	Children have required and tolerated larger doses than *adults*.[3] Change to oral therapy as soon as possible. The IV dose is approximately one-third of the oral dose.[3] **Transplant immunosuppression (bone marrow transplant, cardiac, liver, and renal):** 3–6 mg/kg prior to transplant[3,6] then 2–10 mg/kg/day divided q 8–24 hr[3,7–14] or via continuous infusion.[11,15–20] **Recurrent nephrotic syndrome post-transplant:** Continuous infusion of 3 mg/kg/day titrated to maintain desired serum concentrations.[21] **Prevention of graft versus host disease:** 1–5 mg/kg/day either continuously or in 2 divided doses beginning up to 7 days before transplant with or without titration to desired trough concentrations.[22–27] **Acute myeloid leukemia:** 10 mg/kg followed by a continuous infusion of 30 mg/kg/day for a period of 98 hours as part of a mitoxantrone, etoposide, and cycloSPORINE (MEC) induction regimen.[28] **Inflammatory bowel disease refractory to steroids:** 1.3–4 mg/kg/day by continuous infusion or 5 mg/kg/day by intermittent infusion.[29–34] **Atypical sprue:** Diarrhea resolved and histology improved in a 23-month-old started on 2 mg/kg q 12 hr that was increased to 4 mg/kg q 12 hr.[35]
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal dysfunction.[36] However, nephrotoxicity occurs in 25% to 38% of patients.[3] This may be associated with larger accumulated doses or persistently high trough concentrations.[3] (See Comments section.)
Maximum dosage	Not established.
Additives	Contains polyoxyethylated castor oil 650 mg (Cremophor EL) and 32.9% alcohol by volume.[3]

Suitable diluents	NS, D5W.[3,37]
Maximum concentration	2.5 mg/mL.[3,37]
Preparation and delivery	**Stability:** The extent of cycloSPORINE sorption in PVC is greater when mixed with NS compared to D5W.[37] NS admixtures are considered usable for 6 hours in PVC and 12 hours in glass containers.[38] Storage in glass containers has been recommended.[39] Reconstituted product should be discarded after 24 hours.[3] **Drug delivery system issues:** The Cremophor EL vehicle may leach diethylhexyl phthalate (DEHP), a known hepatotoxin, from PVC bags and tubing.[37] Non-PVC containers and administration sets are recommended, but if PVC bags are used, solutions should be infused immediately to minimize DEHP exposure.[40] A solution with 0.5–2.5 mg/mL of cycloSPORINE had detectable DEHP after >4.5 hours of contact with PVC.[41] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Contraindicated.[3]
Intermittent infusion	Over 2–8 hours.[3–5,13,29–34]
Continuous infusion	1.2–4.5 mg/kg have been given over 24 hours.[15–20]
Other routes of administration	Not indicated.

Comments

Anaphylaxis may be a result of the Cremophor EL vehicle.[3,4,42–44]

Monitoring: Serum concentration monitoring is essential to determining the appropriate dosage. Trough concentrations should be maintained within therapeutic range for the specific assay and transplant type.[3] Trough concentration monitoring is being replaced by a 2-hour postdose concentration because it better approximates $AUC^{(0-4)}$ that correlates with the risk of rejection.[45,46]

Use the same analytical methodology and sample matrix (i.e., whole blood versus plasma) consistently. High-performance liquid chromatography assays are specific for cycloSPORINE. CycloSPORINE metabolites cross-react with polyclonal radioimmunoassay,[47] and fluorescence polarization immunoassay (FPIA) and may result in an overestimation of serum concentrations compared to other methods.[48,49] The FPIA assay may not be reliable in liver dysfunction.[48,50]

Concentrations drawn through a second catheter lumen may be falsely increased when the patient is receiving cycloSPORINE as a continuous infusion through the other lumen.[51]

CycloSPORINE is adsorbed to silicone; blood samples drawn through central venous lines made from silicone may be falsely increased if cycloSPORINE has been infused through them.[52,53]

Drug interactions: CycloSPORINE is principally metabolized by the CYP3A4 isoenzyme and is associated with numerous important drug interactions.[3] Consult appropriate resources for dosing recommendations before combining any drug with cycloSPORINE.

Adverse effects: In renal transplant patients, it is often difficult to determine if a decrease in renal function is due to nephrotoxicity or allograft rejection.[3]

Nephrotoxicity: Responds to a decrease in cycloSPORINE dose, gradual increases in SCr, and a BUN/SCr ≥20.

Rejection: Responds to increased steroids or antilymphocyte globulin, more dramatic increase in SCr, and BUN/SCr <20. Chronic nephrotoxicity may also occur.[3]

Cytomegalovirus Immunoglobulin

Brand names	CytoGam
Medication error potential	None reported by ISMP and USP.[1,2]
Contraindications and warnings	**U.S. boxed warning:** Human immune globulin products have been associated with renal dysfunction, acute renal failure, osmotic nephrosis, proximal tubular nephropathy, and death. These renal effects have been most commonly associated with immune globulin products that contain sucrose as a stabilizer (such as cytomegalovirus immunoglobulin) and daily immune globulin doses of 350 mg/kg or higher. Administer immune globulin products in the lowest concentration and rate of infusion for patients with renal disease, diabetes mellitus, volume depletion, sepsis, paraproteinemia; for patients ≥65 years; and for those receiving other nephrotoxic drugs.[3] **Contraindications:** Known hypersensitivity to the drug, selective immunoglobulin deficiency.[3] **Other warnings:** Carries the possibility for transmission of blood-borne viral agents, including a theoretical risk of Creutzfeldt-Jakob disease, since it is made from human plasma.[3] Hemolysis, thrombotic events, aseptic meningitis syndrome, and transfusion-related acute lung injury have also been reported with the use of immune globulin products.[3]
Infusion-related cautions	Monitor vital signs before, during, and after infusion, and before any rate increases.[3] Flushing, chills, muscle cramps, back pain, fever, vomiting, arthralgias, and wheezing are usually related to infusion rate and may be managed by interrupting the infusion temporarily and restarting at a lower rate. If anaphylaxis or a decrease in blood pressure occurs, the infusion should be discontinued. Epinephrine should be available in case of anaphylaxis.[3]
Dosage	Renal function should be assessed before beginning therapy, as well as at appropriate intervals thereafter, and discontinuation should be considered if renal function deteriorates. Patients should be well hydrated prior to beginning therapy.[3] (See Dosage Adjustment in Organ Dysfunction section.) **HIV-infected patients:** 200 mg/kg alternating biweekly with IV immune globulin.[4] **Transfusions (multiple) in neonates:** 150 mg/kg.[5] **Transplantation** **Bone marrow:** 200 mg/kg given 6 and 8 days prior to transplant and on days 1, 7, 14, 21, 28, 42, 56, and 70 after transplant.[6] **Heart, liver, lung, and pancreas:** 150 mg/kg within 72 hours prior to transplant, 150 mg/kg at 2, 4, 6, and 8 weeks after transplant, and 100 mg/kg at 12 and 16 weeks after transplant.[3,7,8] **Liver and intestine:** 100 mg/kg (on alternating day from ganciclovir) followed by 150 mg/kg at weeks 6 and 8 followed by 100 mg/kg at 12 and 18 weeks after transplant.[8] **Renal:** 150 mg/kg within 72 hours prior to transplant, 100 mg/kg at 2, 4, 6, and 8 weeks after transplant, and 50 mg/kg at 12 and 16 weeks after transplant.[3,9,10] **Infantile cytomegalovirus-associated autoimmune hemolytic anemia:** One dose of 500 mg/kg.[10]
Dosage adjustment in organ dysfunction	Use with caution in patients with renal insufficiency or in those at risk for developing renal insufficiency and infuse at the minimum rate possible.[3] In order to decrease the risk of renal dysfunction, patients should be well hydrated prior to administration.[4]

Cytomegalovirus Immunoglobulin

Maximum dosage	For transplant patients, the manufacturer recommends a maximum dose of 150 mg/kg. 200 mg/kg has been given in HIV infection and multiple transfusions in neonates.[5,7] 500 mg/kg has been administered to two infants for autoimmune hemolytic anemia.[12]
Additives	Each mL contains 50 mg sucrose and 10 mg human serum albumin. Sodium content is 20–30 mEq/L.[3]
Suitable diluents	Predilution is not recommended.[3]
Maximum concentration	50 mg/mL.[3]
Preparation and delivery	**Delivery:** The product should be infused through an in-line filter with a pore size of 15 microns. A 0.2-micron filter is also acceptable. Should be administered through an IV line with a constant infusion pump.[3] **Stability:** Do not shake vial; avoid foaming. Does not contain any preservatives; thus, the infusion should be initiated within 6 hours of entering the vial and be completed within 12 hours of entering the vial.[3]
IV push	Not recommended.[3]
Intermittent infusion	May piggyback into existing infusions of NS or D2.5W, D5W, D10W, D20W (all with or without NaCl) and deliver via an infusion device at no more than 1:2 dilution.[3] **Initial dose**[3]**:** 15 mg/kg/hr for 30 minutes. If no adverse effects are noted, increase to 30 mg/kg/hr for 30 minutes and then to maximum rate of 60 mg/kg/hr. **Subsequent infusions**[3]**:** 15 mg/kg/hr for 15 minutes. If no adverse effects are noted, increase to 30 mg/kg/hr for 15 minutes and then to a maximum rate of 60 mg/kg/hr. Volume should not exceed 75 mL/hr.[3]
Continuous infusion	Not reported.
Other routes of administration	Not recommended.[3]
Comments	Vaccinations with live virus vaccines (measles, mumps, rubella, varicella) should be deferred for 3 months after infusion.[3]

DACTINomycin

Brand names	Cosmegen
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP and USP report that DACTINomycin has been confused with DAPTOmycin; no patient harm resulted.[2,3]
Contraindications and warnings	**U.S. boxed warning:** DACTINomycin should be administered under the supervision of an experienced physician. The drug is highly toxic; both the powder and solution should be handled with care. Inhalation of vapors or dust and contact with skin and mucous membranes should be avoided. Do not use or handle during pregnancy. Special precautions should be in place and reviewed prior to handling due to the toxic properties of DACTINomycin (corrosivity, carcinogenicity, mutagenicity, and teratogenicity). DACTINomycin is highly corrosive and will damage soft tissue if extravasation occurs (see Infusion-Related Cautions section); DACTINomycin extravasation has resulted in contracture of the arm in at least one case.[4] **Contraindications:** Known hypersensitivity to the drug or to any component of this product. Should not be administered around the time of infection with chicken pox or herpes zoster.[4] **Other warnings:** Veno-occlusive disease (especially in children less than 48 months), myelosuppression, dermatological reactions, emesis, and secondary malignancies.[4,5] DACTINomycin should not be used in infants <6 months based on a higher incidence of side effects.[4] (See Comments section.)
Infusion-related cautions	Extravasation will result in severe soft tissue damage. If extravasation is suspected, discontinue infusion and apply, ice to the affected area intermittently for 15 minutes 4 times daily for 3 days.[4] (See Appendix E for additional information regarding extravasation treatment.)
Dosage	Consult individual protocol for complete dosing information. DACTINomycin is used as a component of combination therapy for several malignant pediatric solid tumors. DACTINomycin has also been used in patients with nephroblastoma, malignant melanoma, and osteosarcoma. Dosage should be based on body surface area for obese or edematous patients.[4] (See Appendix A.) Suggested regimens for different disease states include the following: **Wilms tumor, rhabdomyosarcoma, Ewing sarcoma:** 15 mcg/kg/day IV for 5 days in combination with chemotherapeutic agents.[4–10] **Osteosarcoma:** 600 mcg/m^2 IV days 1, 2 and 3, in combination with chemotherapeutic agents. [11] **Metastatic nonseminomatous testicular cancer:** 1000 mcg/m^2/day IV on day 1 with cyclophosphamide, bleomycin, vinblastine, and cisplatin.[4,12] **Gestational trophoblastic neoplasia:** 12 mcg/kg/day IV for 5 days as monotherapy or 500 mcg IV on days 1 and 2 as part of a combination regimen with etoposide, methotrexate, folinic acid, vincristine, cyclophosphamide, and cisplatin.[4,13,14] **Regional perfusion in locally recurrent and locoregional solid malignancies:** 50 mcg/kg for lower extremity or pelvis; 35 mcg/kg for upper extremity.[4]

Dosage adjustment in organ dysfunction	Not established.
Maximum dosage	The manufacturer recommends that dosages should not exceed 15 mcg/kg/day or 400–600 mg/m^2/day for 5 days per 2-week cycle.[4]
Additives	Mannitol 20 mg.[4]
Suitable diluents	Reconstitute with SW; further dilution with D5W, NS.[4,15]
Maximum concentration	500 mcg/mL.[4,15]
Preparation and delivery	**Preparation:** Both the powder and solution can cause severe damage when in direct contact with the skin or through inhalation. Use caution when preparing. Reconstitute by adding 1.1 mL of SW (without preservative). Use of SW containing preservatives is not recommended as it results in precipitation formation.[4,15] Once reconstituted the solution (500 mcg/mL) can be added to a suitable infusion solution.[4] **Delivery:** Binds to cellulose filters; therefore, avoid in-line filtration. Adsorbs to glass and plastic so DACTINomycin should not be given by continuous infusion.[4,15]
IV push	The desired dose of reconstituted drug may be injected into the tubing of a running infusion of D5W or NS.[4,15]
Intermittent infusion	The desired dose of reconstituted drug may be further diluted with D5W or NS or may be injected into the tubing of a running infusion of D5W or NS.[4,15]
Continuous infusion	Not reported.
Other routes of administration	DACTINomycin is highly corrosive and will damage soft tissue. Do not administer as IM or SC injection.[15]
Comments	**Significant adverse effects:** DACTINomycin has been associated with the development of hepatic veno-occlusive disease in children <48 months.[4,16] DACTINomycin has been associated with an increased risk of dermatological adverse effects when used concomitantly with or after radiation.[4] Risks may be increased when radiation involves mucous membranes or when DACTINomycin is administered within 2 months of radiation for right-sided Wilms tumors. DACTINomycin is associated with a moderate (30% to 90%) risk of emesis.[17] Patients should receive antiemetic therapy to prevent acute and delayed nausea and vomiting. The recommended therapy is a 5HT3 receptor antagonist in combination with dexamethasone every day chemotherapy is administered.[17,18] These agents may be continued for up to 4 days after chemotherapy administration for the prevention of delayed nausea and vomiting. Breakthrough medications should also be offered. **Monitoring:** Monitor CBC with differential and platelets, liver function tests, and renal function tests.[4,5] **Laboratory interference:** May interact with the bioassay for determination of antibacterial drug levels.[4]

Daptomycin

Brand names	Cubicin
Medication error potential	Cubicin has been confused with Cleocin[1] and daptomycin with dactinomycin.[1,2]
Contraindications and warnings	**Contraindications:** Daptomycin is contraindicated in patients with known hypersensitivity to the drug.[3] **Warnings:** Myopathy and rhabdomyolysis have been reported with daptomycin use. Patients should be monitored for muscle pain and weakness. Creatine phosphokinase (CPK) should be monitored at least weekly and more frequently in patients receiving concomitant HMG-CoA reductase inhibitors, who have renal impairment, or who have had an increased CPK with daptomycin therapy. CPK elevations may occur more frequently when dosed more than once per day.[3] Hypersensitivity reactions have been reported. If allergic reactions occur daptomycin should be stopped and appropriate measures taken.[3] Eosinophilic pneumonia has been reported 2–4 weeks after starting daptomycin therapy. If this occurs daptomycin should be stopped and systemic steroid therapy is recommended.[3] Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[3]
Infusion-related cautions	No information available.
Dosage	**Daptomycin has not been well studied in children. The following are pediatric doses currently being used in clinical trials:** **Single dose pharmacokinetic studies** **3–24 months:** 6 mg/kg.[4] **2–6 years:** 4–10 mg/kg.[4,5] **7–11 years:** 4–8 mg/kg.[4,5] **12–16 years:** 4–6 mg/kg.[4,5] **Safety and efficacy study** **2–6 years:** 9 mg/kg q 24 hr.[6] **7–11 years:** 7 mg/kg q 24 hr.[6] **12–17 years:** 5 mg/kg q 24 hr.[6] **Published case reports, small case series, and pharmacokinetics studies** **Premature infants:** 12 mg/kg/day divided q 12 hr[7–10] or 6 mg/kg q 24 hr.[11] **2–6 years:** 4–10 mg/kg q 24 hr.[12,13] ***Adults*** **Complicated skin infections:** 4 mg/kg q 24 hr for 7–14 days.[3] **Bacteremia including those with right-sided endocarditis:** 6 mg/kg q 24 hr for 2–6 weeks.[3]

Daptomycin

Dosage adjustment in organ dysfunction	When CrCl is <30 mL/min, the dosing interval should be increased to q 48 hr. Patients receiving dialysis should also receive daptomycin every 48 hours dosed after completion of dialysis.[3] One reference recommends pediatric dosing should be decreased to 4 mg/kg q 24 hr if GFR is 10–29 mL/min, and 4 mg/kg q 48 hr if GFR <10 mL/min.[14]
Maximum dosage	15–22 mg/kg/day have been given successfully to neonates.[7,15]
Additives	Sodium hydroxide for pH adjustment.[3]
Suitable diluents	NS.[3,16]
Maximum concentration	50 mg/mL.[3]
Preparation and delivery	**Stability:** Reconstituted vials and infusion bags are stable at room temperature for 12 hours and under refrigeration for 48 hours.[3,16] **Compatibility:** Compatible with NS and LR.[3,16] Should not be reconstituted with dextrose-containing solutions.
IV push	Over 2 minutes.[3]
Intermittent infusion	Infuse up to 20 mg/mL[16] over 30 minutes.[3,16]
Continuous infusion	Not recommended.
Other routes of administration	2.5 mg in 5 mL NS has been administered intraventricularly.[17]
Comments	**Monitoring:** CPK should be monitored at least weekly.[3] **Drug interactions:** Concomitant administration with HMG-CoA reductase inhibitors may result in elevated CPK levels.[3] **Laboratory interference:** Falsely-prolonged prothrombin time and elevated international normalized ratio have been reported when certain reagents are used for the assay.[3]

Darbepoetin

Brand names	Aranesp
Medication error potential	Look-alike, sound-alike drug names. USP reports that darbepoetin has been confused with dalteparin; no patient harm resulted. USP reports that Aranesp has been confused with Aralast and Aricept; no patient harm resulted.[1]
Contraindications and warnings	**U.S. boxed warning:** Erythropoiesis-stimulating agents (ESAs) carry boxed warnings for increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence. In patients with renal failure, ESAs should be given to achieve and maintain hemoglobin (Hb) concentrations of 10–12 g/dL, as increased mortality and serious cardiovascular events have occurred in two clinical trials when targeting higher Hb concentrations (i.e., 13–14 g/dL).[2] ESAs have shortened survival and/or increased tumor progression in clinical cancer trials (breast, head and neck, lymphoid, non-small cell lung, and cervical cancers). Use the lowest dose possible to avoid transfusions, use only for anemia in combination with chemotherapy, and discontinue when chemotherapy is completed. ESAs should not be given to patients on myelosuppressive therapy if the anticipated outcome is cure.[2] **Contraindications:** Uncontrolled hypertension, known hypersensitivity to the drug or any of its components, and pure red cell aplasia that begins after treatment with darbepoetin or other erythropoietin protein drugs.[2] **Other warnings:** Hypertension and seizures have occurred in patients with chronic renal failure receiving darbepoetin. Pure red cell aplasia and severe anemia have also occurred. Antibody-mediated pure red cell aplasia occurred in patients with hepatitis C infection receiving ESA in combination with antiviral therapy. ESA therapy should be withheld in any patients with antibody-mediated anemia.[2]
Infusion-related cautions	Rare serious allergic reactions, including rash and urticaria, have been reported.[2] In patients with latex allergy, be aware that the needle cover of the prefilled syringe contains dry natural rubber (a latex derivative).[2]
Dosage	To ensure the erythropoietic response, iron status should be evaluated and supplemental iron prescribed if stores are low. Transferrin saturation should be ≥20% and ferritin should be ≥100 ng/mL.[2] Target Hb range should be 10–12 g/dL.[2] **Anemia in (nonmyeloid or solid tumor) cancer**[3–6]**:** Safety and efficacy of darbepoetin in anemia of childhood cancer has not been established. The following dosages have been used in *adults*: 1–4.5 mcg/kg SC once weekly.[3,4] 3–9 mcg/kg SC q 2 wk.[5] 4.5–15 mcg/kg SC q 3 wk.[6] Do not treat if Hb >10 g/dL. If Hb has increased by <1 g/dL during initial 6 weeks of therapy (with adequate iron stores), then increase dose by 25% every week (up to 4.5 mcg/kg/dose) until at target Hb concentration. If Hb has increased >1 g/dL over a 2-week period or the Hb concentration reaches a level needed to avoid transfusion, then decrease dose by 40%. If Hb exceeds level needed to avoid transfusion, then temporarily hold therapy.[2]

Dosage *(cont.)*

One pharmacokinetic study in pediatric cancer patients gave 2.25 mcg/kg SC once weekly for up to 6 doses.[7]

Darbepoetin is not indicated for use in patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure.[2]

Anemia of chronic renal insufficiency[2,8–12]

1–18 years: 0.25–0.75 mcg/kg IV or SC once weekly or once q 2 wk.[2,8–10,13,14] (See Comments section.)

Adjust dosage (monthly) to achieve and maintain a target Hb concentration of 10–12 g/dL.[2]

If Hb has increased <1 g/dL during initial 4 weeks of therapy (with adequate iron stores), then increase dose by 25% q 4 wk until at target Hb. If the Hb increases by more than 1 g/dL in 2 weeks or the Hb is increasing and approaching 12 g/dL, then decrease dose by 25%.[2]

<8 kg (use not established): 0.5 mcg/kg once weekly was given to six infants with renal dysplasia, three on peritoneal dialysis.[11] Doses were increased or decreased by 25% to maintain Hb concentrations 10–11 g/dL. After 20 weeks, in three stable patients (one on peritoneal dialysis), Hb ranged from 11.7–13.5 g/dL, and doses were 0.17 or 0.25 mcg/kg q 4 wk or 0.34 mcg/kg q 3 wk. In three medically unstable patients, Hb ranged from 8.5–9.7 g/dL, and doses were 1.06–1.24 mcg/kg weekly. Investigators concluded that individualized dosing was warranted.

Peritoneal dialysis, 0–17 years (use not established): 0.45 mcg/kg once weekly given intraperitoneally at the end of peritoneal dialysis session.[15]

Anemia of prematurity (use not established): Erythroid progenitor cells in cord blood, fetal marrow, and fetal liver were equally stimulated by erythropoietin and darbepoetin.[16] In a pharmacokinetics study, a single dose of 1 or 4 mcg/kg SC increased erythropoiesis in preterm infants <1500 g.[17] Another pharmacokinetic study evaluated an IV dose of 4 mcg/kg in 10 neonates 704–3025 g and found a shorter half-life and more rapid clearance than has been noted in children.[18] In addition, both the immature reticulocyte count and the absolute reticulocyte count increased.[18]

Dosage adjustment in organ dysfunction

Patients with chronic renal insufficiency who are not on dialysis may require lower maintenance doses.[2]

Maximum dosage

Not established. Doses up to 8 mcg/kg once weekly and 15 mcg/kg q 3 wk have been used in *adults* with cancer.[5,6]

Additives

Available in two formulations. The albumin solution contains 2.5 mg human albumin and 8.18 mg sodium chloride in water for injection per mL.[2] The polysorbate solution contains 0.05 mg polysorbate and 8.18 mg sodium chloride in water for injection per mL.[2]

Suitable diluents

Darbepoetin should not be diluted.[2]

Maximum concentration

500 mcg/mL.[2]

Preparation and delivery

Vigorous shaking and/or exposure to light may physically denature the glycoprotein and inactivate the molecule.[2]

Do not administer with any other IV drug.[2]

Darbepoetin

IV push	Rapid, within 15 seconds.[8]
Intermittent infusion	Not reported.
Continuous infusion	Not reported.
Other routes of administration	SC route is preferred except in patients on hemodialysis when IV administration is preferred.[2] IM is not indicated.
Comments	**Monitoring:** Monitor hemoglobin (Hb) weekly until target is achieved, then monthly. Do not increase the dose more frequently than every 4 weeks.[2] **Other:** One study in children with chronic renal insufficiency based the initial dose on current recombinant human erythropoietin dosing (rHuEPO dose/200 = darbepoetin weekly dose).[10] Investigators noted an excessive increase in Hb in six of seven children evaluated. The two youngest received 3.6 and 2.79 mcg/kg weekly and developed hypertension (Hb was >13 g/dL). The dose was held for 2 weeks and restarted at half the previous dose. At the end of 6 months, doses in all seven patients ranged from 0.37–0.69 mcg/kg weekly. This is consistent with the manufacturers' current recommendations.[2] Another study used a conversion ratio of 100 units rHuEPO to 0.42 mcg darbepoetin.[13] The manufacturer recommends giving darbepoetin once weekly if the patient was receiving rHuEPO 2–3 times per week and once every 2 weeks if the patient was receiving rHuEPO once per week.[2] Darbepoetin (0.42–0.66 mcg/kg SC weekly in combination with ferric gluconate or iron dextran over 4–18 months) has been given to four pediatric patients (age 10–16 years) with anemia associated with recessive dystrophic epidermolysis bullosa.[19] Inform patients of risks associated with ESA therapy. Medication guides, available from the manufacturer, should be given to all patients receiving ESA therapy at home.[2]

Deferoxamine Mesylate

Brand names	Desferal Mesylate
Medication error potential	Look-alike, sound-alike drug names. Desferal has been confused with DexFerrum; however, no patient harm resulted.[1]
Contraindications and warnings	Contraindicated in severe renal disease or anuria since both deferoxamine and iron chelate are renally excreted.[2]
Infusion-related cautions	Flushing, urticaria, hypotension, and shock may occur, particularly with rapid IV administration.[2–5] Anaphylaxis may occur.[2]
Dosage	**Iron exposure** **Acute iron ingestion:** While the manufacturer states that IM administration is the preferred route and should be used for all patients not in shock,[2] toxicology literature supports the IV administration of deferoxamine for acute iron poisoning.[3] 15 mg/kg/hr by continuous infusion[2,3,6–9] until urine is a normal color for 24 hours[7,8] or until clinical status and laboratory values normalize. Alternatively, an initial dose of 20 mg/kg or 600 mg/m^2 (IM or slow IV infusion) followed by 10 mg/kg or 300 mg/m^2 q 4 hr for 2 doses.[10] Subsequent doses of 10 mg/kg or 300 mg/m^2 q 4–12 hr are given as clinically needed.[10] 5 mg/kg/hr by continuous infusion, in combination with aggressive fluid resuscitation and inotropic support, successfully lowered serum iron concentrations in a 7-week-old preterm (27 weeks gestational age) neonate. The dose could not be increased due to hypotension.[11] **Chronic iron overload due to transfusion-dependent anemias:** 14–98 mg/kg/day over 8–12 hours.[12–14] A recent study gave high-dose (15 mg/kg/hr for 48 hours) q 2 wk for a mean duration of 19.6 months to 27 patients with sickle cell disease.[15] Dose should be individualized based on the degree of iron overload. **Aluminum-related disorders in kidney disease (use not established):** To avoid deferoxamine induced adverse effects (neurotoxicity), it should not be given to patients with an initial serum aluminum >200 mcg/L. Treat these patients with intensive high-flux dialysis until serum aluminum is <200 mcg/L.[16] **Deferoxamine test:** Measure serum aluminum before infusion and 2 days later (before next dialysis session). 5 mg/kg of deferoxamine should be given during last hour of dialysis session. Doses as low as 0.5 mg/kg have also been used.[16] **Aluminum rise <300 mcg/L and no side effects after test:** 5 mg/kg IV over last hour of hemodialysis, once per week for 2 months; high-flux hemodialysis 44 hours after dose. **Aluminum rise ≥300 mcg/L or side effects after test:** 5 mg/kg IV over 1 hour; give 5 hours before hemodialysis, once per week for 4 months; high-flux hemodialysis after deferoxamine. **Hemochromatosis (neonatal):** Patients often receive a cocktail of medications that includes deferoxamine 30 mg/kg/day infused over 8 hours until the serum ferritin <500 mcg/L.[17] This is palliative therapy as early liver transplantation is essential for survival.

Dosage adjustment in organ dysfunction	Product labeling states that deferoxamine is contraindicated in patients with severe renal dysfunction or anuria because the drug and the iron chelate are renally eliminated.[2] Another reference states that therapy should continue in renal failure; however, no guidelines were suggested for adjustment of the infusion rate.[3] One reference noted that the dose should be decrease dose by 25% to 50% in *adults* with GFR between 10 and 50 mL/min and to avoid use with GFR <10 mL/min.[18]
Maximum dosage	Total amounts should not exceed 6 g/24 hr,[2] but larger doses have been used in clinical practice.[3] 16 g was infused to an *adult* with transfusion-related iron overload over 24 hours without apparent adverse effects.[19] While doses >50 mg/kg/day (up to 235 mg/kg/day) have been used,[12–14,20–22] doses <50–60 mg/kg/day are recommended to avoid neurotoxicity.[23] (See Comments section.) 2520 mg or 210 mg/kg/day (15 mg/kg/hr over 14 hours) has been given safely to an 18-month-old with acute iron intoxication (serum iron concentration 447 mcg/dL).[24]
Additives	None reported.
Suitable diluents	SW (for reconstitution). NS, ½NS, D5W, LR (for dilution).[2,25]
Maximum concentration	250 mg/mL.[2]
Preparation and delivery	**Preparation:** Available in 500-mg and 2-g vials of sterile drug in dry form. For IM injection, reconstitute the 500-mg and 2-g vials with 2 mL and 8 mL, respectively, to yield solutions providing deferoxamine mesylate 213 mg/mL.[25] For IV infusion, reconstitute the 500-mg and 2-g vials with 5 mL and 20 mL, respectively, to yield solutions providing deferoxamine mesylate 95 mg/mL.[25] **Delivery system issues:** Stable at room temperature in polypropylene syringes (14 days); PVC infusion cassette reservoirs (9–17 days); and natural rubber elastomeric reservoirs (14 days).[25] **Stability:** Do not store vials above 25°C.[2] Diluents other than SW and refrigeration may cause precipitation.[25] Turbid solutions should not be used.[2] Although reconstituted solutions may be stored for 24 hours at room temperature, the manufacturer recommends immediate use due to a lack of preservative.
IV push	Not recommended.[2] (See Infusion-Related Cautions section.)
Intermittent infusion	Do not to exceed 15 mg/kg/hr or 125 mg/hr once the first 1000 mg has been infused.[2]
Continuous infusion	Do not to exceed 15 mg/kg/hr or 125 mg/hr once the first 1000 mg has been infused.[2]
Other routes of administration	Some recommend IM administration as the preferred route for acute iron ingestion in patients not in shock.[2] May be given via SC infusion with a portable controlled-infusion device.[25]

Deferoxamine Mesylate

Comments

Significant adverse effects: Hypotension is a common adverse effect and generally relates to the rate of administration.[9] Vision and hearing impairment has been attributed to chronic chelation treatment with deferoxamine.[4,6,12,14,20,21,23,26] Doses that exceed a 0.025 "therapeutic index" (ratio of mean daily dose in mg/kg divided by serum ferritin) increase the risk for sensorineural hearing loss.[14] Cessation of chelation therapy and/or dosage reduction frequently leads to improvement.[4,12,21,26]

A pulmonary syndrome (i.e., acute respiratory distress syndrome [ARDS]) has been associated with length of therapy[22,27–31] and total daily doses >6 g.[32] Another study suggests that the pulmonary abnormalities are related to inadequate chelation.[33] Intermittent infusions for <24 hours have been recommended.[29,34]

Nephrotoxicity has also been reported.[35] Adequate hydration decreases the incidence of this adverse effect.[35]

Neurotoxicity has been reported.[4,12–14,20,21,23,26] Large doses may exacerbate neurologic dysfunction (i.e., seizures) in patients with aluminum-related encephalopathy.[2]

Growth retardation has occurred in patients with low ferritin concentrations who receive large doses of deferoxamine.[36] To minimize this, the dose should not exceed 25–30 mg/kg.[36] Following reduction in the deferoxamine dose, growth velocity may partially return to pretreatment rate. Pediatric patients should be monitored for body weight and growth every 3 months.[2]

Rare adverse effects: Deferoxamine has been associated with an increased risk of infection. This is particularly true for *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*.[2] Mucormycosis has also been reported, particularly in dialysis patients.[2,16] Patients should be monitored for fever, abdominal complaints, and pharyngitis, and the drug should be discontinued until any suspected or documented infection resolves.[2]

Other: Patients with chronic iron overload usually become vitamin-C deficient. *Adults* with chronic iron overload have developed cardiac impairment following concomitant treatment with deferoxamine and large doses of vitamin C.[2] The abnormalities reversed when vitamin C was discontinued.[2] Recommended daily vitamin C doses should not be exceeded.

Urine may not always be a vin rosé color following administration of deferoxamine, even when iron overload is present.[37]

Dexamethasone Sodium Phosphate

Brand names	Decadron, generic
Medication error potential	Look-alike, sound-alike drug names. USP reports that dexamethasone has been confused with betamethasone, doxazosin, methadone, and methylprednisolone, and patient harm did not occur. Dexamethasone has been confused with dexmedetomidine, and patient harm occurred. Decadron has been confused with Depacon and Dexedrine, and patient harm did not occur.[1]
Contraindications and warnings	**Contraindications:** Patients with systemic fungal infections except in the management of drug reactions to amphotericin B.[2] Patients with hypersensitivity to any component in the product.[2] Live virus (live attenuated influenza; measles, mumps, and rubella [MMR]; oral polio; varicella; rotavirus; smallpox; zoster) vaccinations should not be given during treatment with immunosuppressive doses of glucocorticoids.[2] (See Drug Interactions in the Comments section.) **Warnings:** Anaphylactoid reactions have been reported and those with a prior history of such reactions require appropriate precautions.[2] Patients on chronic steroid therapy may require increased doses during stressful situations.[2] Supraphysiologic doses of corticosteroids may result in suppressed pituitary-adrenal function, so therapy of more than a few days should be decreased gradually.[2,3] Immunosuppression and an increased risk for infection are possible during steroid therapy.[2]
Infusion-related cautions	None noted.
Dosage	**Prevention or treatment of bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) in very low birth weight (VLBW) infants** **AAP recommendations:** High-dose dexamethasone regimens (0.5 mg/kg/day) reduce BPD/CLD but are associated with short- and long-term adverse outcomes including neurodevelopmental impairment and are not recommended. In patients >1 week of age, low-dose regimens (<0.2 mg/kg/day) may facilitate extubation with fewer adverse outcomes, but there is insufficient evidence to make a recommendation.[4] (See Other in the Comments section.) **DART trial regimen (all doses divided q 12 hr):** 0.15 mg/kg/day for 3 days followed by 0.1 mg/kg/day for 3 days and then 0.05 mg/kg/day for 2 days (cumulative dose 0.89 mg/kg).[5] **Lower dose regimens:** Initial dose 0.05 mg/kg/day then tapered over 9 days to provide a cumulative dose of 0.24 mg/kg[6] or 0.05 mg/kg/day for 10 days followed by alternate-day doses for 6 days (cumulative 0.65 mg/kg).[7] (See Other in the Comments section.) **Prevention of post-extubation stridor or laryngeal edema in high-risk patients:** (Dexamethasone given prior to extubation was not beneficial during uncomplicated airway management.)[8,9] **Preterm infants:** 0.25 mg/kg q 8 hr for 3 doses.[10] **Infants and children:** 0.5 mg/kg (max 8 mg) at 4 hours before extubation, at the time of extubation, then at 6 and 12 hours after extubation successfully prevented laryngeal edema or stridor in one study.[11] Multiple other studies using similar dosing regimens (e.g., 0.5 mg/kg [max 10 mg] q 6 hr for 6 doses beginning 6–12 hours before anticipated extubation) found no benefit.[8,12–14]

Dosage *(cont.)*

Nausea and vomiting prevention

Prevention of chemotherapy-induced nausea and vomiting (in addition to 5-hydroxytryptamine 3 antagonists)[15,16]**:** Various regimens published. 10 mg/m^2 q 12 hr on chemotherapy days[17]; 8 mg/m^2 prior to chemotherapy followed by either 4 mg/m^2 q 6 hr for 2 doses or 8 mg/m^2 q 4 hr for 2 doses[18]; 10 mg/m^2/day (max 10 mg/day).[19] *In adults*, for highly or moderately emetogenic chemotherapy, dexamethasone is recommended on days 1–3 or 1–4; for low emetogenic chemotherapy, only 1 dose prior to chemotherapy is recommended.[15]

Prevention of radiation-induced nausea and vomiting (in addition to 5-hydroxytryptamine 3 antagonists)[15]**:** 5-day course of dexamethasone during fractions 1–5.

Prevention of postoperative nausea and vomiting: In children undergoing surgery for strabismus, 0.25 mg/kg was as effective as 0.5 mg/kg and 1 mg/kg given during induction.[20] In another study in 135 children undergoing strabismus surgery, 1 intraoperative dose of 1 mg/kg dexamethasone (max 25 mg) was as effective as ondansetron.[21] For tonsillectomy, single preoperative doses of 0.15 mg/kg (max 8 mg),[22] 0.5 mg/kg (max 8 mg),[23,24] and 1 mg/kg (max 50 mg)[25] have been effective.[26]

Acute laryngotracheitis (croup): For those who are unable to take PO, 0.6 mg/kg (max 16 mg) IM or IV as a single dose is recommended.[27,33] In children with moderate-to-severe croup, 0.15 mg/kg (max 3 mg; n = 20) was as effective as 0.6 mg/kg (max 12 mg; n = 21).[31]

Meningitis, bacterial: 0.15 mg/kg q 6 hr for 2–4 days of antibiotic therapy was effective in reducing hearing loss in those with *Haemophilus influenzae* type b (Hib) disease. However, the outcome in patients with pneumococcal meningitis treated with dexamethasone has been either worse or no different than controls.[34,35] With the use of Hib and pneumococcal conjugate vaccines, both Hib and pneumococcal meningitis have decreased.[36,37] A Cochrane review published in 2010 analyzing >4000 patients (n = 2,524 ages 1 month to 16 years) found that corticosteroids prevented hearing loss in children, and, despite the declining prevalence of Hib and pneumococcal causes, recommended dexamethasone 0.6 mg/kg/day for 4 days in patients with bacterial meningitis.[38]

Asthma: Methylprednisolone sodium succinate is the recommended parenteral glucocorticoid for asthma.[39] However, a randomized controlled trial found a single dexamethasone dose (0.6 mg/kg IM; max 15 mg) as effective as a 5-day course of oral prednisolone for patients with moderate exacerbations discharged home from the ED.[40]

Cerebral edema, elevated intracranial pressure due to brain tumor: A loading dose of 1–2 mg/kg[33,41] followed by 1–1.5 mg/kg/day (max 16 mg/day) divided q 4–6 hr.[41] Not recommended for treatment of elevated intracranial pressure in pediatric patients with traumatic brain injury.[42]

Septic arthritis: 0.15 mg/kg/dose IV q 6 hr for 4 days reduced the duration of IV antibiotics, local inflammatory signs, and acute phase reactants in a randomized, placebo-controlled trial in 49 children 6 months to 18 years old. No adverse effects were noted.[43]

Intractable epilepsy (West syndrome or electrical status epilepticus in slow-wave sleep): Pulse therapy with 20 mg/m^2 IV daily for 3 days with 4 weeks between each cycle appeared as effective as adrenocorticotropic hormone therapy in a small retrospective study. Positive responses were observed from 1 week up to 10 weeks after initiation.[44]

Dosage adjustment in organ dysfunction

Those with cirrhosis of the liver or who are hypothyroid may have an exaggerated response.[2] Dosing adjustment is not necessary for renal dysfunction.[45]

Maximum dosage

Not established.[2]

Dexamethasone Sodium Phosphate

Additives	Some products contain sodium sulfite, sodium metabisulfite, and/or benzyl alcohol. Preservative-free products are available.[2,46,47] (See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.)
Suitable diluents	D5W, NS.[2,48]
Maximum concentration	Undiluted (10 mg/mL).[2]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.
IV push	Over 1 to several minutes.[2]
Intermittent infusion	The dose can be infused intermittently.[2]
Continuous infusion	Not indicated.
Other routes of administration	Formulations of 4 or 10 mg/mL may be used IM or IV.[2,28,29,40] A formulation of 4 or 10 mg/mL can be given as intra-articular, intrasynovial, intralesional, or as a soft tissue injection.[2,51]
Comments	**Other:** While early dexamethasone (initiated during first week of life) facilitated extubation in VLBW infants, the Vermont Oxford Network Steroid Study Group concluded that neither CLD nor mortality is favorably affected.[50] Cochrane and systematic reviews report benefits including reductions in CLD and extubation failure with early dexamethasone[51,52] and reductions in mortality, CLD, and extubation failure with late dexamethasone (initiated after first week of life).[53,55] However, Cochrane and systematic reviews raise concerns about serious adverse effects.[51–55] Dexamethasone is associated with a worsened neurological outcome including an increased risk of cerebral palsy,[51,56] poor weight gain,[50,51,57] GI bleeding,[51] intestinal perforation,[51,57] hyperglycemia, hypertension, and hypertrophic cardiomyopathy.[51] While selected populations may derive benefit from dexamethasone, clear recommendations cannot be made. The use of dexamethasone should be reserved for infants >1 week of age who cannot be weaned from mechanical ventilation, and the dose and duration should be minimized.[4,53] Recommendations published in 2003 designed to improve neonatal outcomes suggested avoiding dexamethasone in the first 10 days of life.[58] For patients requiring dexamethasone, recommendations were 0.2–0.3 mg/kg/day divided q 12 hr for 48 hours, and if treatment was extended beyond 48 hours, the dose should be halved q 48 hr with a maximum treatment length of 10 days.[58] The updated AAP Policy Statement published in 2010 recommends against high-dose regimens (0.5 mg/kg/day) and suggests that low-dose regimens (<0.2 mg/kg/day) may facilitate extubation with fewer adverse outcomes; however, it finds insufficient evidence to make a recommendation. Studies evaluating low-dose regimens have been encouraged.[4]

Comments *(cont.)*

The Dexamethasone: A Randomized Trial (DART) investigators conducted a randomized, multicenter, controlled trial of low-dose dexamethasone (initial dose 0.15 mg/kg/day and tapering over 10 days) in 70 extremely low birth weight infants after the first week of life. Dexamethasone facilitated extubation, shortened duration of mechanical ventilation, and did not cause any short-term adverse effects.[5] Two small trials evaluating even lower dosing regimens have also been published. In 16 extremely premature babies who had failed extubation attempts, a 9-day tapering regimen starting with 0.05 mg/kg/day (cumulative 0.24 mg/kg) appears to successfully facilitate extubation.[6] A retrospective matched study comparing low-dose dexamethasone to placebo in 76 ventilator-dependent babies $<$30 weeks gestational age or $<$1500 g finds dexamethasone 0.05 mg/kg/day for 10 days followed by alternate-day doses for 6 days (cumulative 0.65 mg/kg) superior to placebo for improving respiratory function and extubation rates, with no increase in hypertension, hyperglycemia, or GI perforation/hemorrhage.[7]

Adverse effects: Musculoskeletal effects, fluid and electrolyte abnormalities, cataracts, and hyperglycemia.[2] Patients with diabetes may be at particular risk for hyperglycemia.

Drug interactions: Drugs that enhance hepatic clearance (e.g., phenytoin, phenobarbital, carbamazepine, and rifampin) may decrease blood levels and lessen physiologic activity. Drugs that inhibit hepatic clearance may increase dexamethasone concentrations.[2,41] Dexamethasone may decrease the serum concentration of caspofungin, possibly necessitating increased dosing for caspofungin.[41] Steroids may potentiate neuromuscular blockade; monitor patients receiving concomitant nondepolarizing neuromuscular blocking agents.[41]

Live virus vaccines may be given 1 month after ending a $\geq$2-week course of high-dose systemic corticosteroids (2 mg/kg/day of prednisone or its equivalent, or 20 mg/day if $>$10 kg.[59]

Dexmedetomidine HCl

Brand names	Precedex
Medication error potential	ISMP high-alert medication (moderate sedation agent) that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that dexmedetomidine has been confused with dexamethasone and patient harm occurred. Precedex has the potential to be confused with Cerebyx.[2]
Contraindications and warnings	**Warnings:** Because of known cardiovascular effects, including bradycardia, sinus arrest, and hypotension, patients should be continuously monitored.[3,4] Slowing the rate of the infusion may modify the cardiovascular effects.[3] Transient hypertension has been noted during loading dose infusion.[3] During infusion, some patients may be arousable and alert when stimulated and this alone should not be considered lack of efficacy.[3] Abrupt withdrawal symptoms include nervousness, agitation, and headaches with increased blood pressure and can occur up to 48 hours following discontinuation of a continuous infusion.[3] (See Significant Adverse Effects in the Comments section.)
Infusion-related cautions	See Contraindications and Warnings section.
Dosage	**Sedation in premature neonates:** A case report describes successful addition of dexmedetomidine in a baby born at 24 weeks gestational age, birth weight 730 g, requiring high-frequency ventilation who developed agitation refractory to standard sedatives. On day of life 9, a bolus of 0.5 mcg/kg over 10 minutes and an infusion of 0.25 mcg/kg/hr were initiated. The infusion reached a max of 0.7 mcg/kg/hr; duration of infusion was 19 days. The infusion was eventually tapered off by 0.1 mcg/kg/hr q 12–24 hr.[5] **Procedural sedation:** Higher doses may be required if used as the sole sedative.[6,7] **Bolus:** 0.5–3 mcg/kg over 5–10 minutes.[4,6–18] About one-third of patients may need more than 1 bolus dose and/or additional sedatives during longer procedures such as MRI scans.[18] One study examined rapid boluses (0.25 mcg/kg or 0.5 mcg/kg over 1 minute) in 12 patients with heart transplants and found transient increases in systemic and pulmonary pressures along with bradycardia.[19] **Infusion:** 0.3–2 mcg/kg/hr.[4,6,7,9–12,14–18] **Intraoperative or preoperative adjunct to general anesthesia** **Bolus:** 0.3–4 mcg/kg over 3–10 minutes.[20–27] **Infusion:** 0.7–2 mcg/kg/hr.[20,21,24] Dexmedetomidine was found to reduce postoperative pain/agitation[20,22–24,27] in surgeries including hypospadias repair, strabismus repair, and tonsillectomy/adenoidectomy. **Sedation in critically ill children requiring mechanical ventilation (noncardiac population)** **Bolus:** 0.25–0.5 mcg/kg.[28] **Infusion:** 0.2–1.4 mcg/kg/hr.[28–30]

Dosage *(cont.)*	Three groups of 10 children per group received either continuous infusion midazolam, a bolus of 0.25 mcg dexmedetomidine/kg over 5 minutes followed by 0.25 mcg/kg/hr, or 0.5 mcg dexmedetomidine/kg over 5 minutes followed by 0.5 mcg/kg/hr. The dexmedetomidine or midazolam infusions were increased if 3–4 doses of morphine were required within 8 hours.[28] Less morphine and fewer infusion rate changes were required by either of the dexmedetomidine groups than the midazolam comparator.[28] To minimize midazolam use and to facilitate weaning from mechanical ventilation, an initial continuous infusion of 0.2 ± 0.2 increased to 0.5 ± 0.2 mcg/kg/hr (used with fentanyl or morphine) based on adequacy of sedation was used for 3–75 hours in 17 infants and children.[29] None experienced significant changes in blood pressure or heart rate.[29] **Sedation in cardiothoracic surgery population** **Bolus:** 0.35–1 mcg/kg.[31–33] **Infusion:** Typical dosing range is 0.2–1 mcg/kg/hr.[31–36] **Facilitation of opioid weaning:** A 6-month-old infant and a 7-year-old child sedated for 8 weeks and 15 days prior to cardiac transplant and for 4 weeks and 3 days after, respectively, were given 1 mcg/kg over 10 minutes followed by 0.8–1 mcg/kg/hr and 0.5–1 mcg/kg/hr for 10 and 8 days, respectively. Doses were then weaned as tolerated over 6 days and 24 hours.[37] Seven patients, 3–24 months old, received a bolus of 0.5 mcg/kg and an infusion of 0.5 mcg/kg/hr to treat opioid withdrawal. The infusion was weaned off by 0.1 mcg/kg/hr q 12–24 hr.[38] **Treatment of opioid-induced hyperalgesia:** 0.2–0.7 mcg/kg/hr, often as part of a multicomponent regimen to allow reduction of opioids (n = 3 and n = 1 pediatric patients in two reports).[39,40]
Dosage adjustment in organ dysfunction	Dose reduction should be considered in patients with hepatic impairment.[3]
Maximum dosage	**Procedural sedation:** Bolus of 3 mcg/kg[7]; infusion of 2 mcg/kg/hr.[16,41] **Sedation during mechanical ventilation** **Noncardiac:** Bolus dose of 0.5 mcg/kg.[5,28] Two case reports describe maximum reported infusion doses. In one case, 1.4 mcg/kg/hr was used in one patient requiring prolonged mechanical ventilation and high doses of benzodiazepines and opiates.[30] A similar case describes an infant who received 2 mcg/kg/hr during mechanical ventilation.[42] **Cardiac population:** Bolus of 1 mcg/kg[31,32]; infusion of 1 mcg/kg/hr.[31]
Additives	Contains 9 mg sodium chloride/mL.[3]
Suitable diluents	NS is recommended. Also compatible with D5W, LR, and mannitol 20%.[3,43]
Maximum concentration	4 mcg/mL.[3]
Preparation and delivery	The 100-mcg/mL vial must be diluted in NS for infusion.[3]
IV push	Not indicated.[3]

Dexmedetomidine HCl

Intermittent infusion	4 mcg/mL.[3] Bolus (loading) doses are typically administered over 5–10 minutes.[3,28]
Continuous infusion	4 mcg/mL.[3] Manufacturer labeling limits recommended duration to 24 hours.[3] Longer durations have been reported (75 hours,[29] 378 hours,[44] 46 days,[40] and over 2 months[30]).
Other routes of administration	Not indicated. However, various other routes have been reported. **Caudal:** Dexmedetomidine (1 or 2 mcg/kg) has been combined with bupivacaine and given via caudal block in patients from 0.5–6 years of age in Cairo, Egypt.[45,46] **Regional anesthesia:** 1 mcg/kg with bupivacaine was administered as greater palantine nerve block for cleft lip/palate repair.[47] **Intranasal:** 1 mcg/kg produced more sedation than oral midazolam in children undergoing a minor surgical procedure in Hong Kong.[48] Intranasal dexmedetomidine has also been used in *adults*.[49] Following nasal administration of 1 mcg/kg in children, the median onset was 25 minutes and median duration was 85 minutes.[50] All studies used a solution of 100 mcg/mL, either undiluted or diluted with NS to a final volume of 0.4 mL/dose. **SC:** Seven patients, 6 months to 4 years old, received infusions for 4–7 days for drug withdrawal.[51] **IM:** 1–4 mcg/kg (using 4-mcg/mL injection); patients were premedicated with topical lidocaine patches 20 minutes before injection.[52] **Buccal:** 3–4 mcg/kg (using undiluted injection) administered 60 minutes before surgery in patients 1–7 years old.[53]
Comments	Dexmedetomidine appears to have less effectiveness in infants <1 year old.[28,34] **Significant adverse effects:** Bradycardia (high 40s to low 50s) was reported in a 5-week-old girl with trisomy 21 who had a large atrioventricular septal defect and was also receiving digoxin.[54] Up to 30% of patients undergoing sedation for a CT scan experienced bradycardia during the bolus (2 mcg/kg) or infusion (1 mcg/kg/hr).[6] In a second study examining sedation for MRI, while less than 4% of patients experienced bradycardia (bolus of 2–3 mcg/kg and infusion of 1–2 mcg/kg/hr), the heart rates at times fell more than 20% below the lower limit of normal.[7] No interventions were necessary for the bradycardia episodes.[6,7] Acute withdrawal occurred in a 2-year-old who had received an infusion (0.3–0.8 mcg/kg/hr) for 7 days during and after cardiac surgery. Withdrawal symptoms resolved with reinstitution of the infusion and did not recur with gradual tapering (by 0.1 mcg/kg/hr q 8 hr).[55] Another report of withdrawal, including seizures, occurred in an 8-week-old after a 3.5-day infusion (0.5–2 mcg/kg/hr). Symptoms improved after starting clonazepam and reinstituting the infusion; the infusion was tapered off over 9 hours.[42] A patient who had received an infusion for over 2 months (up to 1.4 mcg/kg/hr) was successfully tapered off by decreasing the infusion by 0.06 mcg/kg/hr each day for 2 weeks.[30] Twelve children with supraventricular tachycardia who underwent cardiac electrophysiology study and ablation under anesthesia were given 1 mcg/kg over 10 minutes followed by a continuous infusion of 0.7 mcg/kg/hr for 10 minutes. During the infusion, sinus and atrioventricular nodal function were depressed, heart rate decreased, and arterial blood pressure increased.[56] A subsequent study in 51 postoperative cardiac surgery patients found no significant differences in electrocardiographic measurements taken before and during infusion, other than an expected trend toward decreased heart rate.[31] A case report described loss of pacemaker capture during infusion.[57]

Comments *(cont.)*

Transient hypertension may occur due to the acute increase in peripheral vasoconstriction during higher (>2 mcg/kg) bolus doses[41,58] or during higher (>1 mcg/kg/hr) dose infusions.[41,58,59] Hypertension occurred more frequently in infants who required more than 1 loading dose to achieve effective initial sedation scores for procedures.[41] A recommendation for limiting hypertension in the postoperative cardiac population is to limit bolus doses to 0.5 mcg/kg.[58]

A severe rash was noted within 4 hours of beginning a continuous infusion in a critically ill, intubated *adult*. The infusion was discontinued and by 48 hours the rash had disappeared. According to the Naranjo adverse drug reaction probability scale, the relationship with dexmedetomidine was probable.[60]

Pharmacokinetics: The terminal half-life in 24 children from 2–12 years of age was 1.8 hours.[61] In 10 postsurgical, critically ill children from 0.4–7.9 years of age, the terminal half-life was 2.65 ± 0.88 hours (range: 1.59–4.27 hours).[62] A study evaluating population pharmacokinetics in children from 4 days to 14 years found that clearance in neonates was about one-third that of *adults* and reached 87% of *adult* values at 1 year of age.[63] In a pooled analysis, clearance in postoperative cardiac surgical patients was 27% lower than all other patients.[64] The terminal half-life in *adults* is ~2 hours.[3]

Impact on EEG: A bolus of 2 mcg/kg with an infusion of 1 mcg/kg/hr in patients with intractable epilepsy induced an EEG pattern resembling Stage II sleep.[65] Another report indicates that dexmedetomidine had less effect on EEG than midazolam.[8]

Dextrose

Brand names	Various manufacturers
Medication error potential	ISMP high-alert medication (dextrose concentrations of 20% or greater) that has an increased risk of causing significant patient harm if it is used in error.[1]
Contraindications and warnings	**Contraindications:** Concentrated dextrose solutions should not be used when intracranial hemorrhage is present.[2] Dextrose injection should not be infused with blood through the same infusion set because red cell pseudoagglutination may occur.[2] **Warnings:** Significant hyperglycemia and hyperosmolality may occur with rapid infusion of concentrated dextrose solutions.[2]
Infusion-related cautions	Infusion of hypertonic dextrose solutions is irritating to veins and can cause phlebitis when infused via peripheral vein. Usually, the concentration infused peripherally is limited to 11.5% to 12.5% dextrose.[3,4] Abrupt withdrawal of concentrated dextrose solutions may result in hypoglycemia. This may be avoided by gradual decreases in the rate of infusion.[2] If an IV line infusing concentrated dextrose becomes nonfunctional, a peripheral IV can be used to infuse a lower concentration of dextrose (i.e., D5W, D10W).
Dosage	**Hypoglycemia:** Neonatal hypoglycemia is a metabolic emergency; serious neurological injury can occur if normal blood glucose is not established.[5] **Preterm neonates:** 0.1–0.2 g/kg (1–2 mL/kg of 10% dextrose) followed by 6–8 mg/kg/min.[4,6–8] (See Comments section.) **Term neonates and infants ≤6 months:** 0.2–0.5 g/kg (2–5 mL/kg of 10% dextrose or 1–2 mL/kg of 25% dextrose) administered slowly followed by 6–12 mg/kg/min.[5,7–14] Neonates with persistent hypoglycemia may require >12–15 mg/kg/min.[5,8] For neonatal hypoglycemia, titrate dextrose to achieve blood glucose concentration 40–50 mg/dL.[9,14] **Infants >6 months and children:** 0.5–1 g/kg (5–10 mL/kg of 10% dextrose or 2–4 mL/kg of 25% dextrose)[4,10,15] administered slowly followed by 3–7.5 mg/kg/min. **Pediatric resuscitation:** 10% dextrose, 5–10 mL/kg; 25% dextrose, 2–4 mL/kg; 50% dextrose, 1–2 mL/kg[15] **Hyperkalemia (with insulin):** 0.2–1 g/kg (3.2–16 mg/kg/min) initially in combination with insulin dosed at 4–5 g dextrose for every 1 unit of regular insulin.[4,16] One study reported safe and effective use of a compounded multicomponent solution containing 3000 mg calcium gluconate, 150 g dextrose, 30 units regular insulin, and 100 mEq sodium acetate (final volume approximately 556 mL; final dextrose concentration 27%) infused at 2 mL/kg/hr for 1 hour followed by 1 mL/kg/hr to treat hyperkalemia in 21 patients. The solution resulted in a dextrose infusion of 0.54 g/kg/hr for 1 hour then 0.27 g/kg/hr until resolution of hyperkalemia.[17]
Dosage adjustment in organ dysfunction	In liver failure the glucose requirement may be increased due to depletion of glycogen stores.
Maximum dosage	1 g/kg not to exceed 0.8 g/kg/hr in *adults*.[2] 15–25 mg/kg/min (0.9–1.5 g/kg/hr) has been given to hyperinsulinemic neonates.[5,18]

Dextrose

Additives	Contains no more than 25 mcg/L of aluminum.[2,19,20]
Suitable diluents	Concentrated dextrose should be diluted in compatible parenteral fluids including PN.
Maximum concentration	**Peripheral:** 12.5% dextrose (except for emergency situations).[4] **Central venous lines:** Usually 25% dextrose;50% dextrose in emergencies.[4] **Resuscitation:** 25% in neonates, infants, and children. 50% has been used in adolescents and *adults*.[15]
Preparation and delivery	Dilute to desired concentration in compatible electrolyte solution or PN.
IV push	0.2 g/kg over 1 minute.[4,12] Too rapid infusion may result in hyperglycemia.[2] (See Comments section.)
Intermittent infusion	Over 30 minutes to 2 hours (treatment of hyperkalemia).[4]
Continuous infusion	4.5–15 mg/kg/min.[10,18]
Other routes of administration	Not for SC or IM administration.[2] May be given IO during resuscitation.[15]
Comments	**Monitoring:** Blood glucose concentrations should be monitored often during treatment for hypoglycemia and hyperkalemia.[12,15] Hyperglycemia causes osmotic fluid shifts that may result in rapid dehydration and intraventricular hemorrhage in neonates.[7] Following hyperglycemia, rebound hypoglycemia can occur because of stimulation of insulin secretion.[7,10,12] The osmolarity of body fluids is about 310 mOsm/L. The osmolarity of 10% dextrose is 505 mOsm/L, and 25% dextrose is 1330 mOsm/L.[4]

Diazepam

Brand names	Valium, Zetran
Medication error potential	High-alert medication associated with an increased risk of causing significant patient harm if used in error.[1] Look-alike, sound-alike drug names. Confusion has been reported with alprazolam, clonazepam, DiaBeta, Ditropan, doxepin, lorazepam, midazolam, oxazepam and temazepam.[2] Valium with Vicodin have also been confused.[2] Errors with diltiazem have resulted in patient harm.[2]
Contraindications and warnings	**Contraindications:** Should not be used in patients with a known hypersensitivity to diazepam or other benzodiazepines.[3] Contraindicated in those with acute narrow angle glaucoma and in open angle glaucoma unless patient is receiving appropriate therapy.[3] **Warnings:** Administer cautiously to very ill patients or those with limited pulmonary reserve due to possible apnea and/or cardiac arrest.[3] Do not administer to patients in shock, coma, or in acute alcoholic intoxication with depression of vital signs.[3] When used with a narcotic analgesic, the dosage of the narcotic should be reduced by at least one third and given incrementally.[3] May precipitated tonic status epilepticus in patients receiving diazepam for absence (petit mal) status or absence (petit mal) variant status.[3] Withdrawal symptoms (e.g., convulsions, tremor, abdominal and muscle cramps, vomiting, and sweats) may occur following abrupt discontinuation. The more severe symptoms are usually seen in patients who received excessive doses over an extended period of time.[3] (See Infusion-Related Cautions section.)
Infusion-related cautions	Resuscitative equipment, including ones necessary to support respiration, should be readily available.[3] Thrombophlebitis and infiltration-associated tissue necrosis may develop.[3–5] To reduce the possibility of venous thrombosis, phlebitis, local irritation, and (rarely) vascular impairment, inject slowly into a large vein.[3] (See IV Push section.)
Dosage	Flumazenil should be readily available for reversal. (See Comments section, Other Routes of Administration section, and Flumazenil monograph.) **Procedural sedation:** *Midazolam* is the preferred benzodiazepine because of its rapid onset and short duration.[6–8] (See Midazolam monograph.) 0.05–0.1 mg/kg slowly titrated q 15–30 min[7,8] to desired effect or 0.04–0.3 mg/kg/dose q 2–4 hr to a maximum of 0.6 mg in 8 hours.[9] The lowest effective dose should be used. **Status epilepticus:** *Lorazepam* is the preferred IV benzodiazepine for use in pediatric patients.[10–12] (See Lorazepam monograph.) **Neonates:** Not recommended due to benzyl alcohol content and prolonged sedation due to an inability to metabolize.[3] (See Additives section and Comments section.) **Infants and children:** 0.1–0.4 mg/kg repeat q 5–10 min for 2–3 doses.[10,11,13–18] (See Maximum Dosage section.) Although continuous infusion diazepam has been used, midazolam is preferred for continuous administration. (See Continuous Infusion section and Midazolam monograph.) **Tetanus (muscle spasms):** The manufacturer recommends 1–2 mg/dose q 3–4 hr if >30 days and <5 years of age and 5–10 mg/dose q 3–4 hr if ≥5 years of age.[3] A series of 19 neonates received 20–40 mg/kg/day (0.83–1.67 mg/kg/hr) as continuous infusion accompanied by intermittent bolus doses of 5–10 mg.[19] Three neonates (7–10 days) were given 48–50 mg/kg/day divided into 2-hour intervals.[20] Three children (6–12 years) received 7.5–15 mg/kg/day divided into 2-hour intervals.[20] (See Pharmacodynamics in Comments section.)

Diazepam

Dosage adjustment in organ dysfunction	No adjustment required in renal dysfunction[3,21]; however, prolonged administration to patients with renal dysfunction may result in propylene glycol toxicity.[22,23] Use cautiously in hepatic dysfunction.[3]
Maximum dosage	1 mg/kg, not to exceed a total dose of 5 mg in children <5 years or 10 mg in children ≥5 years of age.[3] 2.7 mg/kg was given without adverse effects to a neonate[24] and 1.7 mg/kg/hr was given via continuous infusion.[25] Large doses given by continuous infusion may produce propylene glycol toxicity. Neonates should not receive doses larger than 1 mg/kg/hr because of benzyl alcohol toxicity.[26] (See Additives section and Comments section.)
Additives	1 mL contains 1.5% benzyl alcohol, 40% propylene glycol, 10% ethyl alcohol, and 5% sodium benzoate and benzoic acid.[27] (See Appendix C for specific information about benzyl alcohol and propylene glycol potential for toxicity.)
Suitable diluents	D5W, LR, or NS.[27] (See Preparation and Delivery section.)
Maximum concentration	5 mg/mL for IV push.[16,22]
Preparation and delivery	**Preparation:** Addition of diazepam to D5W and NS (50 and 200 mg/L) may results in an immediate and persistent yellow precipitate; however, at the same concentrations the addition of the diluent to the diazepam injection results in a cloudy solution that clears.[27] **Delivery system issues:** No significant loss of diazepam following storage in plastic syringes composed of polypropylene and polyethylene.[27] Loss of potency appears to be a function of drug concentration and time. Significant loss due to diazepam sorption (24% loss of potency in 30 min and 80% to 90% loss in 24 hours) has been noted with PVC bags. Diazepam 50 mg/L in D5W and NS was delivered over 7-hours through four types of 0.2-µm membrane filters. Diazepam loss of 7% to 17% was noted in the first 60 minutes; subsequent diazepam levels returned to the original concentration when the binding sites became saturated. **Stability:** Store commercial product at controlled room temperature.[27] In tropical climates, discoloration due to oxidative hydrolytic degradation may occur. Over 4 weeks, there was no loss of drug under simulated summer conditions (26°C to 38°C) in paramedic vehicles.[27] **Photosensitivity:** Protect commercial product from light exposure until ready to use.[27]
IV push	5 mg/mL over ≥3 minutes.[3,27] Rate should not exceed 2 mg/min in infants and children[28] and 5 mg/min in *adults*.[3] Apnea may occur if given too rapidly.[18]
Intermittent infusion	No information available.
Continuous infusion	*Midazolam* is the benzodiazepine of choice for continuous infusion. (See Midazolam monograph.) Rarely used.[26,29] 0.01 mg/kg/min increased by 0.005 mg/kg/min q 15 min to a maximum dosage of 0.03 mg/kg/min.[26] Doses in neonates should not exceed 1 mg/kg/hr due to the risk of benzyl alcohol toxicity.[23]
Other routes of administration	*Midazolam* is the benzodiazepine of choice for IM administration. (See Midazolam monograph.) Undiluted (5 mg/mL) diazepam (osmolality =7775 mOsm/kg) can be given deep into a muscle, but it may cause tissue damage[3–5] and is erratically absorbed.

Diazepam

Comments

Rare adverse effects: Continuous infusion has caused propylene glycol-associated hyperosmolality, increased anion gap and osmolar gap metabolic acidosis (due to lactic acidosis), acute kidney injury, and sepsis-like syndrome.[22,23,30,31] This most frequently occurs in patients with renal dysfunction, who receive prolonged infusions.

Abnormal movements of limbs (e.g., myoclonus or seizures) have been described in premature and full-term neonates given benzodiazepines.[32–34] The movements began a few minutes after a bolus injection and continued for several hours.[32,34]

Drug interactions: Diazepam is a substrate of CYP1A2, 2B6, 2C9, 2C19 (major), and 3A4 (major).[9] It is a weak inhibitor of CYP2C19 and CYP3A4.[9] Consult appropriate resources for dosing recommendations before combining any drug with diazepam.

Pharmacodynamics: Use in neonates is controversial since benzodiazepines may decrease blood pressure and cerebral blood flow velocity.[35] Neonates may also experience prolonged CNS depression because of an inability to biotransform diazepam to an inactive metabolite.[3] Some recommend the initial dose be reduced by 50% in infants <2 months of age[36]; regardless, diazepam should be used cautiously in neonates.

Other: Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for complete or partial reversal of benzodiazepine toxicity.[37] (See Flumazenil monograph.) Although rare (1% to 2%), patients given flumazenil may experience exacerbation of seizure activity, which can range from simple twitching and jerking, to single or multiple seizure events, to status epilepticus.[35,37] Seizures responded to reintroduction of a benzodiazepine or use of an anticonvulsant.[36,37] Because of the presence of flumazenil, larger than normal doses of benzodiazepines may be required.

Digoxin

Brand names

Lanoxin

Medication error potential

High-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1]

Look-alike, sound-alike drug names. Confusion has been reported with Lanoxin and levothyroxine and naloxone.[2]

Contraindications and warnings

Contraindications: Known hypersensitivity to digoxin or other digitalis preparations or ventricular fibrillation.[3]

Warnings: Caution is advised in patients with the following: acute myocarditis or amyloid cardiomyopathy, sinus node disease and atrioventricular (AV) block, chronic constrictive pericarditis, electrical cardioversion (low voltage), electrolyte imbalance, hypo-or hyperthyroidism, hypoxia, renal disease, severe bradycardia, severe heart failure, severe pulmonary disease, sick sinus syndrome, ventricular tachycardia, ventricular premature contractions, and Wolff-Parkinson-White syndrome.[3]

Infusion-related cautions

Inadvertent over administration may occur if a tuberculin syringe is used to measure very small doses.[4,5] Do not aspirate fluid or blood into the syringe containing digoxin because administration of residual drug left in the syringe hub may cause an overdose.[4,5] (See Preparation and Delivery section.)

Dosage

Dosage is based on lean body weight and normal renal function.[3] In general, divided daily dosing is recommended for infants and children.[3] Administer one-half of total digitalizing dose (TDD) initially, one-fourth 8–12 hours after the first dose, and the remaining one-fourth 8–12 hours after the second dose.[6–9] Assess clinical response before administering each dose.[3]

Age	TDD (mcg/kg)	Maintenance Dose (mcg/kg/day)
Premature neonates	15–30[3,5–9]	5–10 divided q 12 hr[6,8,10–14]
Full-term neonates	10–30[3,6,8,9]	8–10 divided q 12 hr[3,8,15]
Infants <2 yr	30–50[7,8,13]	10–12 divided q 12 hr[3,8,15]
Children 2–10 yr	20–35[3,6,8]	8–10 divided q 12 hr[8,15]
Children >10 yr	8–12[3]	2–3 divided q 12 hr[3,16] or given once daily[17]

Because large variability exists in patient response to initial and maintenance doses, individualize dosage based on serum digoxin concentration and clinical response.

Dosage adjustment in organ dysfunction

If CrCl is 30–50 mL/min, give 75% of the dose; if 10–29 mL/min, give 50% of the normal dose or give a normal dose q 36 hr; and if CrCl is <10 mL/min, give 25% of a normal dose or give a normal dose q 48 hr.[18] Dosing should be optimized by measuring serum digoxin concentrations.

Maximum dosage

TDD should not exceed 1 mg.[19] Maintenance dose generally approximates 30% of TDD. Maintenance doses rarely exceed 10 mcg/kg/day or 0.25 mg/day.[3–15]

Additives

Pediatric (100 mcg/mL) and *adult* (250 mcg/mL) injection contains propylene glycol 40% and alcohol 10%.[3,20] (See Appendix C for specific information about propylene glycol potential for toxicity.)

Digoxin

Suitable diluents	D5W, NS, ½NS, D5½NS, D5½NS + 20 mEq/L KCl or LR.[20]
Maximum concentration	100 mcg/mL for pediatric patients and 250 mcg/mL for *adults*.[3]
Preparation and delivery	**Preparation:** For dose volumes <0.1 mL, prepare a 1:10 dilution to improve measurement accuracy. Dilute 0.1 mL of digoxin (100 mcg/mL) with 0.9 mL of saline to make a concentration of 10 mcg/mL. Use the two-syringe technique to make the dilution: draw up the drug in one syringe and the diluent in another. Inject drug into diluent syringe and mix well. This technique avoids "syringe dead space overdose," which can occur when additional fluid is drawn into a drug-containing syringe. Failure to use the two-syringe technique causes drug in the dead space to be drawn up also, and it can result in a significantly larger dose than intended (5 mcg versus 8–12 mcg for digoxin).[4,5,11] Dilute at least fourfold (25 mcg/mL).[3,20] Use of less than a fourfold volume of diluent may result in precipitation.[3] **Stability:** Use digoxin immediately after diluting.[3] Stable in LR, D5½NS+ 20 mEq/L KCl and ½NS for 4–6 hours and stable in D5W and NS for 48 hours.[20] Store at controlled room temperature (25°C). **Compatibility:** See Appendix D for PN compatibility information.[21] **Photosensitivity:** Protect from light exposure until ready to use.[3,20]
IV push	Undiluted (100 mcg/mL) over at least 5 minutes or longer.[3] Rapid IV infusion causes systemic and coronary arteriolar vasoconstriction.[3]
Intermittent infusion	≤25 mcg/mL[3,20] and infuse over >5 minutes.[3] (See Comments section.)
Continuous infusion	No information available.
Other routes of administration	IM administration is not recommended because of local pain, irritation, and tissue damage.[20] If it must be given IM, it should be given by deep injection followed by massage of the area.[3] Inject no more than 2 mL (200 mcg) at any one site.[20]
Comments	**Significant adverse effects:** Has been reported to cause virtually every arrhythmia including sinus bradycardia, AV block, sinoatrial (SA) block, atrial or nodal ectopic beats, ventricular arrhythmias, bigeminy, trigeminy, atrial tachycardia with an AV block.[3] **Monitoring:** Serum electrolytes and renal function should be monitored. Hypercalcemia may increase the risk of toxicity.[3] Toxicity may also occur with hypokalemia and hypomagnesemia despite serum digoxin concentrations within the therapeutic range.[3] ECG may assist in the diagnosis of digoxin-associated toxicity. Serum digoxin concentrations will be falsely elevated if drawn during the predistribution phase (i.e., within 6 hours of digoxin dose).[8] Serum digoxin concentrations should be obtained at least 6–8 hours after the last dose, regardless of the route of administration or formulation used.[3] "Therapeutic" serum concentrations generally range between 0.8–2 ng/mL. Although toxicity is usually accompanied by values >2 ng/mL, serum concentration must be used in conjunction with clinical symptoms and ECG to confirm diagnosis of digoxin toxicity.

Digoxin

Comments *(cont.)*

Drug interactions: The metabolism of digoxin is not dependent on the cytochrome P-450 system, and it is not known to induce or inhibit the cytochrome P-450 system.[3] Digoxin is a substrate of P-glycoprotein and should be used with caution when administered concomitantly with drugs known to inhibit glycoprotein (e.g., quinidine, verapamil, amiodarone, ketoconazole, and itraconazole).[22] Macrolides (erythromycin and clarithromycin) can increase digoxin bioavailability via inhibition of intestinal flora, which metabolizes digoxin in the gut while simultaneously inhibiting P-glycoprotein. Consult appropriate resources for dosing recommendations before combining any drug with digoxin.

Laboratory interference: Depending on the assay, serum digoxin concentrations may be falsely elevated because of endogenous digoxin-like immunoreactive substances in patients with renal or hepatic dysfunction, neonates, infants, and children.[23-28] Spironolactone may interfere with the digoxin radioimmunoassay.[29] Digoxin immune FAB has been shown to interfere with many radioimmunoassays of digoxin.[30,31] This interference results in a significant overestimation of digoxin serum concentrations. To determine the degree of interference, review the manufacturer specification for the assay used at your institution.

Other: Patients experiencing serious cardiac effects due to digitalis toxicity, may receive digoxin-immune Fab.[3] (See Digoxin Immune Fab monograph.)

Digoxin has been successfully used via transplacental administration to treat fetal supraventricular tachyarrhythmias.[32]

Digoxin Immune Fab

Brand names

Digibind, DigiFab

Medication error potential

Look-alike, sound-alike drug names. Digoxin immune fab may be confused with digoxin.[1]

Contraindications and warnings

Contraindications: Hypersensitivity to digoxin immune Fab, sheep products, or any component of the formulation.[2]

Warnings: If digoxin has been used to treat heart failure, exacerbation of symptoms of heart failure may appear as serum digoxin concentrations fall.[2] (See Comments section.)

Patients allergic to papain, chymopapain, or papaya extracts may be allergic to Fab.[2] Likewise, those with known allergies to dust mite and latex may experience a cross-allergy.[2] Use cautiously in those with hypokalemia, poor heart function (withdrawal of inotropic effect), and/or renal failure.[2]

Infusion-related cautions

Anaphylactoid, hypersensitivity, and febrile reactions have occurred.[2–4] Individuals at high risk for allergy should receive a test dose.[2] Give a 1:100 dilution by mixing 0.1 mL of reconstituted Fab (9.5 mg/mL) in 9.9 mL NS (95 mcg/mL). Inject 0.1 mL of the dilution through 0.22-micron filter intradermally or place one drop on skin and make a ¼ scratch through drop with a sterile needle.[2] Evaluate test site for 20–30 minutes.[2–4] Epinephrine should be immediately available.

Dosage

For manifestations of severe digitalis toxicity unresponsive to other therapies.[2]

Dose should be based on the estimated amount of digoxin or digitoxin ingested or on serum digoxin concentration.[2–4] 38 mg (one vial Digibind) or 40 mg (one vial DigiFab) binds 0.5 mg of digoxin or digitoxin.[2] To calculate the total body load of digitalis, use either[2] of the following:

Dosing method based on estimated amount ingested

For digoxin tablets, oral solution, or IM injection[2,4]

$$\text{Dose in mg} = \frac{(\text{dose ingested (mg)} \times 0.8)}{0.5} \times 38$$

For digitoxin tablets, digoxin capsules, IV digoxin, or IV digitoxin[2,4]

$$\text{Dose in mg} = \frac{\text{dose ingested (mg)}}{0.5} \times 38$$

Digibind dosing based on measured serum *digoxin* concentration[2,4]

Weight (kg)	SDC† 1 ng/mL	SDC† 2 ng/mL	SDC† 4 ng/mL	SDC† 8 ng/mL	SDC† 12 ng/mL	SDC† 16 ng/mL	SDC† 20 ng/mL
1	0.4 mg*	1 mg*	1.5 mg*	3 mg	5 mg	6 mg	8 mg
3	1 mg	2 mg	5 mg	9 mg	14 mg	18 mg	23 mg
5	2 mg	4 mg	8 mg	15 mg	23 mg	30 mg	38 mg
10	4 mg	8 mg	15 mg	30 mg	46 mg	61 mg	76 mg
20	8 mg	15 mg	30 mg	61 mg	91 mg	122 mg	152 mg
40	0.5 vial	1 vial	2 vials	3 vials	5 vials	7 vials	8 vials
60	0.5 vial	1 vial	3 vials	5 vials	7 vials	10 vials	12 vials
70	1 vial	2 vials	3 vials	6 vials	9 vials	11 vials	14 vials
80	1 vial	2 vials	3 vials	7 vials	10 vials	13 vials	16 vials
100	1 vial	2 vials	4 vials	8 vials	12 vials	16 vials	20 vials

*Dilution of reconstituted vial to 1 mg/mL may be desirable.
†SDC = serum digoxin concentration.

Dosage *(cont.)*

DigiFab dosing based on

1) Measured serum *digoxin* concentration[2,4]

Weight (kg)	SDC† 1 ng/mL	SDC† 2 ng/mL	SDC† 4 ng/mL	SDC† 8 ng/mL	SDC† 12 ng/mL	SDC† 16 ng/mL	SDC† 20 ng/mL
1	0.4 mg*	1 mg*	1.5 mg*	3 mg	5 mg	6.5 mg	8 mg
3	1 mg	2.5 mg	5 mg	10 mg	14 mg	19 mg	24 mg
5	2 mg	4 mg	8 mg	16 mg	24 mg	32 mg	40 mg
10	4 mg	8 mg	16 mg	32 mg	48 mg	64 mg	80 mg
20	8 mg	16 mg	32 mg	64 mg	96 mg	128 mg	160 mg

*Dilution of reconstituted vial to 1 mg/mL may be desirable.
†SDC = serum digoxin concentration.

$$\text{Dose in mg} = \frac{\text{serum } \textit{digoxin} \text{ concentration (ng/mL)} \times \text{weight (kg)}}{100} \times 38$$

or

2) Dosing method based on measured serum *digitoxin* concentration[2,4]

$$\text{Dose in mg} = \frac{\text{serum } \textit{digitoxin} \text{ concentration (ng/mL)} \times \text{weight (kg)}}{1000} \times 38$$

or

3) Amount ingested unknown or SDC unavailable[2,4]**:** Give 760 mg (20 vials of 38 mg).

Chronic toxicity and SDC unavailable: Infants and children ≤20 kg, one vial (38 mg) is adequate to reverse most cases of toxicity.[5] If ≥20 kg, give six vials (228 mg).[6]

Dosage adjustment in organ dysfunction

Fab fragments may be eliminated more slowly in patients with renal failure.[2–4]

Maximum dosage

Not established. Following acute ingestion, 760 mg should be sufficient. For chronic ingestion, a single vial (38 mg) should be sufficient for infants and small children (<20 kg) and 228 mg (six vials) should be sufficient for children ≥20 kg and *adults*.[6]

Additives

Processed with papain, which may cause hypersensitivity reactions in patients allergic to papaya, other papaya extracts, papain, chymopapain, or the pineapple enzyme bromelain.[2]

Suitable diluents

SW, NS.[2]

Maximum concentration

9.5 mg/mL.[2]

Preparation and delivery

Stability: Store reconstituted drug at 2°C to 8°C for up to 4 hours.[2] Do not freeze.[5]

IV push

In one study, an 1800-g infant received 160 mg over 5 minutes.[7] May give dose more rapidly in cases of impending cardiac arrest.[2]

Digoxin Immune Fab

Intermittent infusion	1–9.5 mg/mL over 20–60 minutes[2,8–10] through a 0.22-micron filter to remove protein aggregate.[2] After reconstitution, no additional dilution is needed prior to administration.[2] For very small doses, a reconstituted vial can be diluted to 1 mg/mL with 34 mL of NS (Digibind) and 36 mL of NS (DigiFab).[2]
Continuous infusion	No information available.
Other routes of administration	No information available.
Comments	**Monitoring:** Clinical improvement in signs and symptoms associated with digitalis toxicity generally occur in ≤30 minutes following administration of Fab.[2] Complete reversal of cardiac and noncardiac manifestations of toxicity generally occur 3–4 hours after completion of the infusion.[11] Serum potassium should be monitored closely as concentrations may fall rapidly (i.e., within 30 minutes) after initiation of Digibind.[2,9] ECG should be monitored for evidence of conduction disturbances.[2] **Laboratory interference:** Digoxin immune Fab in human serum interferes with many radioimmunoassays for digoxin to produce a significant overestimation of concentration.[4,12–15] This interference precludes the use of serum digoxin concentrations in patients treated with digoxin immune Fab. To determine the degree of interference, review the manufacturer specification for the assay used at your institution. **Other:** Digoxin should not be initiated until Fab fragments have been eliminated from the body.[2–4] This may take several days in those with normal renal function and may take more than a week in patients with impaired renal function.[2–4]

Dihydroergotamine Mesylate

Brand names	D.H.E 45, and generics
Medication error potential	None reported.[1]
Contraindications and warnings	**Contraindications:** Coadministration of ergot alkaloids with potent CYP3A4 inhibitors (e.g., protease inhibitors, macrolide antibiotics, and azole antifungals) may elevate the serum concentrations of dihydroergotamine, which has resulted in vasospasm that causes serious and/or life-threatening peripheral and cerebral ischemia.[2] Cases of amputation have been reported. (See Drug Interactions in the Comments section.) Should not be used with peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure.[2] Do not use within 24 hours of sumatriptan, zolmitriptan, other serotonin agonists, or ergot-like agents; do not use during or within 2 weeks of discontinuing monoamine oxidase inhibitors.[2] Do not use in patients with (1) uncontrolled hypertension; (2) ischemic heart disease, angina pectoris, history of myocardial infarction, silent ischemia, or coronary artery vasospasm including Prinzmetal angina; (3) hemiplegic or basilar migraine; (4) patients with peripheral vascular disease, sepsis, severe hepatic, or renal dysfunction; and (5) following vascular surgery.[2] **Warnings:** Rare reports of increased blood pressure in patients without a history of hypertension.[2] Although rare, there have been reports of pleural and retroperitoneal fibrosis and cardiac valvular fibrosis following prolonged daily use of injectable dihydroergotamine mesylate.[2] Patients who developed cardiac valvular fibrosis also received drugs associated with cardiac valvular fibrosis.[2]
Infusion-related cautions	None reported.
Dosage	*Postmenarche female patients should undergo pregnancy screening prior to first dose of dihydroergotamine.*[3,4] IV dihydroergotamine, given in conjunction with an antiemetic, is an appropriate treatment of severe migraine; however, it should be reserved for patients who do not respond to other drug therapy, including 5-HT_1 selective receptor agonists.[5] Safety and efficacy of dihydroergotamine has not been established in children.[2] One report gave 0.1 mg q 8 hr to a 4-year-old with cyclic vomiting syndrome; however, she developed intestinal ischemia after a total of 8 doses.[6] **Intractable migraine >72 hours (status migraine)** *In large doses, an initial test dose (50% of the appropriate dose for age/weight) was used; if tolerated the remaining dose was administered 30 minutes later.*[5] **Children 6–9 years of age or <25 kg:** 0.1 mg/dose q 6 hr (small dose) up to 0.5 mg/dose q 8 hr (large dose); improvement usually seen within 5 doses; continue until headache-free to a maximum of 16 doses (small dose) or 20 doses (large dose); if no improvement noted after 5 doses, discontinue dihydroergotamine.[3,5] **Children 9–12 years of age:** 0.15 mg/dose q 6 hr (small dose); improvement usually seen within 5 doses; continue until headache-free to a maximum of 16 doses; if no improvement noted after 5 doses, discontinue dihydroergotamine.[3] One study treated children in doses ranging from 0.1–0.5 mg/dose (increasing by 0.05 mg increments as tolerated) repetitively averaging 5 doses.[4] **Children >9 years of age or >25 kg and adolescents:** 1 mg/dose q 8 hr (large dose); improvement usually seen within 5 doses; continue until headache-free to a maximum 20 doses; if no improvement noted after 5 doses, discontinue dihydroergotamine.[3,5]

Dihydroergotamine Mesylate

Dosage *(cont.)*	**Adolescents ≤16 years of age:** 0.2 mg/dose q 6 hr (small dose); improvement usually seen within 5 doses; continue until headache-free to a maximum of 16 doses; if no improvement noted after 5 doses, discontinue dihydroergotamine.[3]
Dosage adjustment in organ dysfunction	Although no studies have been conducted on the effect of renal or hepatic impairment, the manufacturer notes that the drug is contraindicated in patients with severely impaired hepatic or renal function.[2]
Maximum dosage	1.5 mg IV in a 24-hour period in children 6–9 years or <25 kg up to a maximum total dose of 10 mg; 3 mg IV in a 24-hour period in children >9 years or >25 kg and adolescents up to a maximum total dose of 20 mg; both are based on large dose regimen.[3,5] 2 mg in a 24-hour period in *adults* if given IV and 3 mg in a 24-hour period in *adults* if given IM or SC.[2] Total weekly IM, SC, or IV dosage should not exceed 6 mg in *adults*.[2]
Additives	6% ethanol.[2]
Suitable diluents	Administer without dilution.[2]
Maximum concentration	1 mg/mL (commercially available).[2]
Preparation and delivery	**Photosensitivity:** Protect the ampules from light and heat and only administer if the solution is clear and colorless.[2]
IV push	Over 1–2 minutes.[2]
Intermittent infusion	Not applicable.
Continuous infusion	1.5–3 mg of dihydroergotamine in 1000 mL NS has been administered at a constant rate over 24 hours in *adults* and in adolescents 16 years of age and older.[7,8]
Other routes of administration	May be administered IM or SC.[2]
Comments	**Rare adverse effects:** Cases of acute myocardial infarction and arrhythmias have occurred in *adults*.[2] **Drug interactions:** The concurrent administration of potent CYP3A4 inhibitors with dihydroergotamine should be avoided.[2] Examples of potent CYP3A4 inhibitors include antifungals (e.g., ketoconazole and itraconazole), the protease inhibitors (e.g., ritonavir, nelfinavir, and indinavir), and macrolide antibiotics (e.g., erythromycin, clarithromycin, and troleandomycin). Other less potent inhibitors (e.g., saquinavir, nefazodone, fluconazole, grapefruit juice, fluoxetine, fluvoxamine, zileuton, and clotrimazole) should be administered with caution.[2] These lists are not exhaustive; therefore, consult appropriate resources before combining any drug with dihydroergotamine mesylate. **Other:** Metoclopramide (0.2 mg/kg) may be administered 30 minutes prior to dihydroergotamine to reduce the incidence of abdominal discomfort.[2] Concomitant antiemetics may not be needed with IM administration.[9] One study used prochlorperazine or metoclopramide 30 minutes prior to dihydroergotamine for the first 3 doses and then used ondansetron PRN for subsequent doses to decrease risk of extrapyramidal side effects noted with repeated exposure to antidopaminergic drugs.[5]

Diltiazem HCl

Brand names	Cardizem injectable
Medication error potential	High-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1]
Contraindications and warnings	**Contraindications:** Patients with known hypersensitivity to diltiazem or any of its components.[2] Patients with sick sinus syndrome or those with 2nd- or 3rd-degree atrioventricular (AV) block who do not have a ventricular pacemaker, those with severe hypotension or cardiogenic shock, atrial fibrillation or atrial flutter who have an accessory bypass tract, and those with ventricular tachycardia.[2] IV diltiazem and IV beta-blockers should not be infused together or within a few hours of each other.[2] **Warnings:** Cardiac conduction may be affected during infusion. Use with caution in patients with impaired ventricular function. Hypotension may occur with infusion. Acute hepatic injury has been reported after oral diltiazem; thus, IV diltiazem has potential to cause this injury. Transient ventricular premature beats have been noted on conversion of paroxysmal supraventricular tachycardia to normal sinus rhythm and are usually considered to be benign.[2]
Infusion-related cautions	Monitor ECG and blood pressure during infusion.[2] In the event of diltiazem overdose or exaggerated response the following are recommended by the manufacturer[2]: **Bradycardia:** Atropine **High-degree AV block:** Atropine (for bradycardia); fixed-degree block should be treated with pacing **Cardiac failure:** Inotropes **Hypotension**: Vasopressors. While some have recommended that IV calcium be available for the treatment of hypotension,[3,4] the manufacturer states that the response to calcium is inconsistent.[2]
Dosage	*IV diltiazem is not considered first-line treatment of dysrhythmias or hypertension in children as*[5] *only a few reports of IV diltiazem use in children have been published.*[3,6,7] **Atrial tachycardias:** Seven children from 0.6–13 years of age were given 0.25 mg/kg over 5 minutes followed by a continuous infusion of 0.05–0.15 mg/kg/hr for up to 126 hours as a bridge to definitive treatment.[3] In *adults*, 0.25 mg/kg (≤20 mg) over 2 minutes. If the response is inadequate after 15 minutes, a second dose of 0.35 mg/kg (≤25 mg) can be given.[2] In *adults* with atrial fibrillation or atrial flutter, the bolus dose may be followed by a continuous infusion of 5–15 mg/hr for up to 24 hours.[2] **Pulmonary hypertension:** Five neonates on extracorporeal membrane oxygenation were given 1–2 mg/dose BID.[6] The dose was titrated upward to 3–7 mg/dose 4 times daily.[6]
Dosage adjustment in organ dysfunction	Use cautiously in patients with renal or hepatic disease, in particular those taking other drugs metabolized by the CYP3A4 enzyme system.[2]
Maximum dosage	In *adults*, 25 mg (0.35 mg/kg).[2]
Additives	Cardizem Lyo-Ject includes a diluent that contains benzyl alcohol.[2] (See Appendix C for specific information about benzyl alcohol toxicity in neonates.)

Suitable diluents	D5W, NS, D5½NS.[2]
Maximum concentration	5 mg/mL.[2]
Preparation and delivery	The manufacturer recommends refrigeration storage and use within 24 hours of dilution.[2]
IV push	5 mg/mL (undiluted) over 2 minutes.[2]
Intermittent infusion	Not indicated.
Continuous infusion	Has been used in *adults* with atrial fibrillation or atrial flutter.[2] (See Dosage section.)
Other routes of administration	Not indicated.
Comments	**Drug interactions:** Diltiazem is metabolized by the cytochrome P450 isozymes and moderately inhibits the CYP3A4 isozyme.[2] Other drugs that are substrates, inhibitors, or inducers of this enzyme system may have an impact on the side effect profile and efficacy of diltiazem. Drugs with interactions noted by the manufacturer include anesthetics, benzodiazepines, beta-blockers, buspirone, carbamazepine, cyclosporine, digitalis, lovastatin, quinidine, and rifampin.[2] Consult appropriate resources before combining any drug with diltiazem.

DiphenhydrAMINE HCl

Brand names	Benadryl
Medication error potential	DiphenhydrAMINE has been confused with dimenhydrinate and dipyridamole, but no patient harm resulted.[1,2] Patient harm resulted when diphenhydrAMINE was confused with dicyclomine; patient.[2] ISMP recommends the following tall man letters (not FDA-approved): diphenhydrAMINE. Benadryl has been confused with benazepril and Benicar; however, no harm occurred.[2] Patient harm occurred when Benadryl was confused with Bentyl.[2]
Contraindications and warnings	Do not use in patients with a previous hypersensitivity to diphenhydrAMINE or antihistamines with similar chemical structure.[3] Do not use in neonates and preterm infants due to potential CNS effects.[3] Antihistamines should be used with considerable caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy or bladder-neck obstruction.[3]
Infusion-related cautions	Local necrosis has occurred when administered SC or intradermal.[3]
Dosage	**Acute hypersensitivity or dystonic reactions** **Infants and children:** 1–2 mg/kg/dose[4–9] up to 5 mg/kg/day or 150 mg/m^2/day divided q 6 hr.[3]
Dosage adjustment in organ dysfunction	No adjustment in patients with renal dysfunction.[10]
Maximum dosage	50 mg/dose,[4] not to exceed 300 mg/day.[3] In *adults*, the maximum is 100 mg/dose, not to exceed 400 mg/day.[3,11]
Additives	The multidose vial contains 0.1 mg/mL benzethonium chloride.[3,12]
Suitable diluents	D5W, D10W, LR, NS, ½NS, or R.[12]
Maximum concentration	25 mg/mL (IV) and 50 mg/mL (IM).[3]
Preparation and delivery	**Stability:** Stored at room temperature.[12] Freezing should be avoided.[12] No loss of drug was noted when diphenhydrAMINE was stored for 4 weeks in paramedic vehicles under simulated summer conditions (26°C to 38°C).[12] **Compatibility:** For PN compatibility information, please see Appendix D. **Photosensitivity:** Store in light-resistant containers.[12]
IV push	Not given.

Intermittent infusion	Over 10–15 minutes, not to exceed 25 mg/min.[3,12]
Continuous infusion	≤50 mg/mL.[3,12]
Other routes of administration	50 mg/mL may be given by deep IM injection.[3,12] Avoid SC or intradermal injection.[3,12]

Comments

Significant adverse effects: Overdose may result in hallucinations, convulsions, respiratory arrest, arrhythmias, or death.[3]

Although antihistamines may diminish mental alertness, paradoxical hyperactivity may occur in pediatric patients.[3,13]

Laboratory test: May interfere with urine detection of methadone and phencyclidine (false positives); may cause false–positive serum tricyclic antidepressant screen; may suppress the wheal and flare reactions to skin test antigens.[14]

Other: One paper describes adjuvant analgesic therapy with diphenhydrAMINE 25 mg IV q 4 hr in addition to fentanyl patient-controlled analgesia in an 8-year-old patient with end-stage oncologic pain.[15]

DOBUTamine HCl

Brand names	Dobutrex, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP and USP report that DOBUTamine has been confused with DOPamine,[2,3] and patient harm occurred. USP also reports that patient harm resulted when Dobutrex was confused with DOPamine.[3]
Contraindications and warnings	**Contraindications:** Patients with idiopathic hypertrophic subaortic stenosis and patients with previous hypersensitivity to DOBUTamine.[4] **Warnings:** DOBUTamine may increase heart rate or blood pressure (especially systolic blood pressure). DOBUTamine use in patients with atrial fibrillation increases risk of rapid ventricular response; use of digoxin prior to DOBUTamine should be used in patients with atrial fibrillation and a rapid ventricular response. Patients with hypertension are at increased risk of exaggerated pressor response with DOBUTamine. DOBUTamine may also cause ventricular ectopic activity.[4]
Infusion-related cautions	Infiltration or extravasation results in local inflammation and pain. Isolated cases of skin necrosis have been reported.[4,5] Aliquots of phentolamine mesylate (0.1–0.2 mg/kg up to 10 mg in 10 mL NS) should be injected intradermally into the ischemic area.[5] (See Appendix E for additional information regarding extravasation treatment.) Use of a large vein is recommended in neonates.[6] Tachycardia, arrhythmias (premature ventricular contractions), and hypertension may occur, especially at greater infusion rates.[4] The tachycardia produced by DOBUTamine may make it unacceptable for use in children after cardiopulmonary bypass.[7]
Dosage	Correct hypovolemia prior to DOBUTamine administration.[4] **Shock, heart failure:** Initial doses of 0.5–1 mcg/kg/min[4,7,8] titrated every few minutes to desired clinical effect, usually 2–20 mcg/kg/min,[4,5,7–19] up to 25 mcg/kg/min in neonates.[6] Given the wide variability in clearance, doses must be individualized.[8,20,21] (See Pharmacokinetic Considerations in the Comments section.)
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal dysfunction.[22]
Maximum dosage	40 mcg/kg/min has been used; however, this dose is associated with increased risk of toxicity.[4,23]
Additives	Contains sodium bisulfite.[4,24–26] Some premixed solutions may also contain edetate disodium dihydrate,[25] whereas others may not.[26] (See Appendix C for more specific information about potential adverse effects of sulfites.)
Suitable diluents	D5W, D5NS, NS,[4,6,24] D5½NS,[4,24] D10W,[4,24] LR,[6,24] D5LR, ½NS,[24] Isolyte M with dextrose 5%, Normosol-M in D5W, 20% Osmitrol in Water for Injection, or sodium lactate injection.[4] Not compatible with strongly alkaline solutions such as sodium bicarbonate or diluents containing both sodium bisulfite and ethanol.[4]

Maximum concentration	5 mg/mL.[4,24]
Preparation and delivery	Hemodynamic instability may be attributed to significant variability between the ordered dosage and the actual solution concentration of DOBUTamine.[27] **Delivery:** May be filtered through a 0.22-micron filter without significant DOBUTamine loss.[24] **Stability:** DOBUTamine solutions may have a pink discoloration, resulting from oxidation; however, no significant drug loss occurs within the recommended 24-hour storage time.[24] **Compatibility:** For PN compatibility information, please see Appendix D.
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	0.25–5 mg/mL.[4,13,24,25] The Joint Commission recommends the use of standardized concentrations of vasoactive medications.[28] The ISMP and Vermont Oxford Network recommend a standard concentration of 2 mg/mL for neonates.[29]
Other routes of administration	IO administration may be used in postresuscitation stabilization.[5,9,30]
Comments	**Monitoring:** Blood pressure,[4,9] urine output,[4] ECG,[4,9] and cardiac output and central venous pressure, when possible, monitoring should occur continuously throughout therapy. Consider monitoring serum potassium due to the potential risk of hypokalemia.[4] **Pharmacokinetic considerations:** Pediatric pharmacokinetic studies have shown large variability in DOBUTamine clearance; changes in clearance do not appear to be associated with age, weight, underlying disease state, or addition of dopamine infusion.[8,20,21] **Pharmacodynamic considerations:** Long-term infusion (i.e., 3–4 days) has produced tolerance to hemodynamic effects and necessitated dosage increases in *adults*.[31] **Other:** Studies suggest DOBUTamine is less effective than DOPamine in increasing blood pressure in premature neonates.[16,32–34] DOBUTamine produced a greater increase in right and left ventricular output.[16,34] In fluid refractory neonatal septic shock, a combination of DOBUTamine and DOPamine may be necessary.[35]

Dolasetron Mesylate

Brand names	Anzemet
Medication error potential	Look-alike, sound-alike drug names. USP reports that dolasetron has been confused with ondansetron and that Anzemet has been confused with Antivert.[1] ISMP reports that Anzemet has been confused with Avandamet.[2]
Contraindications and warnings	**Contraindications:** Patients with known hypersensitivity to the drug.[3] The IV use of dolasetron is contraindicated in *adult* and pediatric patients for prevention of chemotherapy-induced nausea and vomiting (CINV), due to dose-dependent QT prolongation.[3] **Warnings:** ECG changes can occur and are directly related to blood concentrations of the active metabolite, hydrodolasetron.[3] Use with caution in children with congenital QT syndrome, hypokalemia, or hypomagnesemia, and in children receiving concomitant medications that prolong the QT interval.[3]
Infusion-related cautions	Local pain or burning can occur with infusion.[3]
Dosage	Information is available for children 2 years of age and older.[3] **Prevention of CINV:** Due to increased risk of QTc prolongation, IV use of dolasetron for CINV is contraindicated.[3] **Prevention of postoperative nausea and vomiting:** Usually, 0.35 mg/kg up to 12.5 mg given 15 minutes before cessation of anesthesia.[3,5] A dose of 0.5 mg/kg up to 25 mg given at the time of intubation for tonsillectomy was also effective.[6] **Treatment of postoperative nausea and vomiting:** 0.35 mg/kg up to 12.5 mg administered as soon as nausea or vomiting appears.[3]
Dosage adjustment in organ dysfunction	None required.[3]
Maximum dosage	100 mg.[3]
Additives	Single-use injections contain 38.2 mg mannitol/mL.[3] Multidose vials contain 29 mg of mannitol/mL and 5 mg of phenol/mL.[3]
Suitable diluents	NS, D5W, D5½NS, D5LR, LR.[7]
Maximum concentration	20 mg/mL (undiluted).[3]
Preparation and delivery	0.25–2 mg/mL.
IV push	100 mg over 30 seconds in *adults* (undiluted).[3]

Dolasetron Mesylate

Intermittent infusion	Over 15 minutes.[3]
Continuous infusion	Not indicated.[3]
Other routes of administration	Not indicated.[3]
Comments	None.

DOPamine HCl

Brand names	Generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP and USP report that DOPamine has been confused with DOBUTamine.[2,3] USP also reports that patient harm resulted when DOPamine was confused with Dobutrex.[3]
Contraindications and warnings	**U.S. boxed warning:** Extravasation may cause local ischemia and tissue necrosis.[4] Aliquots of phentolamine mesylate (0.1–0.2 mg/kg up to 10 mg in 10–15 mL NS) should be injected using a fine hypodermic needle into the ischemic area.[4,5] This should be done as soon as possible and within the first 12 hours of noting the extravasation.[4] (See Infusion-Related Cautions section and Appendix E for additional information regarding extravasation treatment.) **Contraindications:** Do not use in patients with pheochromocytoma or in patients with uncorrected tachyarrhythmias or ventricular fibrillation.[4] **Warnings:** Patients who have received a monoamine oxidase inhibitor prior to use of DOPamine will require lower DOPamine doses.[4]
Infusion-related cautions	Central access is preferred; however, peripheral IV access is acceptable during resuscitation.[6,7] A case report suggests that terbutaline may be an effective alternative for the treatment of extravasation of DOPamine when phentolamine is unavailable. A 65-year-old patient experienced resolution of symptoms with local SC injection of terbutaline (1 mg in 10 mL NS). Terbutaline concentration based on extent of extravasation, for smaller areas of extravasation a 1:1 dilution may be preferred.[8] (See U.S. Boxed Warning in the Contraindications and Warnings section and Appendix E for additional information regarding extravasation treatment.) Two case reports of distal extremity gangrene have been related to DOPamine infusion, and in one neonate the catheter had good blood return and no signs of infiltration or extravasation were present.[9,10] Digital ischemia with sudden onset of extremity cyanosis (without evidence of infiltration) was observed in a 2-week-old neonate after infusing DOPamine via a peripheral line into the left saphenous vein and right hand. The authors suggested that DOPamine be infused through a central line.[11] Infusion through an umbilical artery catheter is not recommended.[12] Caution is advised if infusion through umbilical vessels becomes necessary; vasospastic events have been reported when administered through umbilical vessels.[4]
Dosage	The restoration of intravascular volume should be addressed prior to the administration of DOPamine.[4,6,7,13] **Shock, hypotension:** 2–20 mcg/kg/min.[4–7,14–18] 1–10 mcg/kg/min[4,19–25] increased by 1–10 mcg/kg/min q 10–40 min until desired hemodynamic response is achieved, up to 20 mcg/kg/min.[4,14,16,19,21,24] In critically ill patients, may initiate at 5 mcg/kg/min and increase by 5–10 mcg/kg/min, up to 20–50 mcg/kg/min.[4,26] (See Maximum Dosage section.) **Other:** Low-dose DOPamine (<5 mcg/kg/min) does not appear to prevent or reduce the incidence of acute oliguric renal failure in critically ill patients and is no longer recommended.[27] Furthermore, low doses of DOPamine may suppress respiratory drive, increase myocardial oxygen demand, worsen splanchnic oxygenation, impair GI function, and impair endocrine and immunologic systems.[28]

Dosage *(cont.)*	Doses of 5–10 mcg/kg/min stimulate beta-receptors and are used for inotropic response.[29] Doses >10 mcg/kg/min stimulate alpha-receptors and are used to increase blood pressure, heart rate, and peripheral vascular resistance.[4,29] Infusions >20 mcg/kg/min are associated with an increased risk for dysrhythmias.[30] They may also result in peripheral, renal,[4,21] and splanchnic vasoconstriction and ischemia[6,26]; epinephrine, norepinephrine, or dobutamine should be used concomitantly if continued inotropic support is needed.[26]
Dosage adjustment in organ dysfunction	DOPamine clearance is decreased in children with renal or hepatic dysfunction.[4,31] Other information suggests no adjustment required in renal dysfunction; titrate dose to desired clinical effect.[32]
Maximum dosage	Usually 20 mcg/kg/min, with occasional use up to 50 mcg/kg/min.[4] Doses exceeding 50 mcg/kg/min have been used in children with advanced circulatory decompensation.[30] Doses as large as 125 mcg/kg/min have been administered to neonates.[26]
Additives	Contains sodium bisulfite.[4,33] (See Appendix C for more specific information about potential adverse effects of sulfites.)
Suitable diluents	D5LR, D5NS, D5½NS, D5W, D10W, LR, or NS.[33] Not compatible with strongly alkaline solutions such as sodium bicarbonate (inactivates DOPamine).[4,33]
Maximum concentration	Usually 3.2 mg/mL.[4] Concentrations up to 6 mg/mL have been infused into large veins (i.e., central vein) of extremely fluid-restricted patients.[34]
Preparation and delivery	**Preparation:** Significant variability between the ordered dosage and the actual solution concentration of DOPamine may occur and account for hemodynamic changes when infusates are replaced. Failure to consider the HCl salt in the stock drug accounts for some of the inaccuracy in preparation.[35] **Delivery:** May be filtered through a 0.2-micron filter without significant DOPamine loss.[33] **Compatibility:** For PN compatibility information, please see Appendix D.
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	0.4–3.2 mg/mL.[4,33] The Joint Commission recommends the use of standardized concentrations of vasoactive medications.[36] The ISMP and Vermont Oxford Network recommend a standard concentration of 1.6 mg/mL for neonates.[37]
Other routes of administration	IO administration may be used in post-resuscitation stabilization.[6,38]

DOPamine HCl

Comments

Significant adverse effects: A 16-year-old patient with pulmonary vascular obstructive disease developed suprasystemic pressure in the right ventricle during DOPamine infusion. It was suggested that DOPamine may be contraindicated in patients with this underlying disease.[39] In a blinded, crossover trial in 19 children (2–54 months of age) requiring inotropic support after cardiac surgery, DOPamine in doses >7 mcg/kg/min caused pulmonary vasoconstriction. The authors concluded that DOPamine should not be used in infants with increased pulmonary vascular resistance secondary to pulmonary hypertension.[40]

An evaluation of 594 children undergoing cardiovascular surgery found that a younger age, longer cardiopulmonary bypass time, and infusion of DOPamine or milrinone were associated with the development of junctional ectopic tachycardia.The authors suggest that DOPamine be discontinued in those who develop this condition.[41]

Monitoring: Blood pressure, urine output, ECG, and cardiac output, when possible. Monitoring should occur continuously throughout therapy.[4,26]

Pharmacokinetic considerations: Studies using a first-order kinetic model were unable to relate clearance to age.[31,42] Using a nonlinear model, clearance varied according to concentration, and increased weight (but not age) was related to a decreased clearance.[43] Still another study reported that clearance is almost 2 times greater in those <2 years old.[44]

Other: A prospective study in 20 preterm infants with arterial hypotension refractory to volume therapy noted that dobutamine or DOPamine (10 mcg/kg/min) increased mean arterial pressure and decreased superior mesenteric artery resistance and proposed that the risk for developing necrotizing enterocolitis during infusion would be reduced.[45]

Use may reversibly inhibit secretion of thyroid-stimulating hormone, prolactin, and growth hormone.[26,46]

Doripenem

Brand names	Doribax
Medication error potential	ISMP reports that Doribax has been confused with Zovirax.[1]
Contraindications and warnings	**Contraindications:** Patients with known allergies to doripenem or to other carbapenems or anaphylaxis to beta-lactams[2] **Warnings** **Allergic reactions:** Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[2] These are more likely in patients who are sensitive to multiple allergens or other beta-lactams.[2] **Superinfection:** Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea, which has been reported and may range in severity from mild diarrhea to fatal colitis. Antibiotic use that is not for the treatment of *C. difficile* may need to be discontinued.[2]
Infusion-related cautions	Phlebitis may occur.[2]
Dosage	**Doripenem has not been well studied in children. The following are pediatric doses currently being used in clinical trials:** **Neonates and infants (clinical trials)** **<8 weeks old:** 5 mg/kg (single dose study).[3] **≤12 weeks old:** 30 mg/kg/day divided q 8 hr (CSF study).[4] **12 weeks to 1 year old:** 90 mg/kg/day divided q 8 hr (CSF study).[4] **Infants and children (clinical trials)** **3 months to 18 years old:** 60 mg/kg/day divided q 8 hr, up to 500 mg/dose.[5–7] ***Adults:*** 1500 mg/day divided q 8 hr.[2]
Dosage adjustment in organ dysfunction	If CrCl >50 mL/min, no dosage adjustment is necessary. If CrCl is 30–50 mL/min, give half the normal dose q 8 hr. If CrCl is >10 but <30 mL/min, give half the normal dose q 12 hr.[2] Hemodialysis may remove approximately 50% from plasma.[8]
Maximum dosage	1 g/dose in *adults*.[9,10]
Additives	None.
Suitable diluents	NS, D5W.[2,11]
Maximum concentration	4.5 mg/mL.[2]

Doripenem

Preparation and delivery	**Preparation:** Vials are reconstituted with 10 mL SW or NS. Suspension must be further diluted with NS or D5W.[2,11] **Stability:** After dilution with NS, may be stored up to 72 hours under refrigeration.[2] **Compatibility:** Compatibility with other drugs has not been established.[2]
IV push	Not recommended.
Intermittent infusion	Administer over 1 hour.[2,11] Extended 4-hour infusions have been recommended for *adult* patients.[9,10,12]
Continuous infusion	Not administered by this method.
Other routes of administration	None.
Comments	**Significant adverse effects** **Rare adverse effects:** Although seizures are reported with carbapenem use, it appears less frequent with doripenem.[13–15] **Drug interactions:** Doripenem reduces serum concentrations of valproic acid.[2,16] Probenecid decreases doripenem clearance.[2]

Doxapram HCl

Brand names	Dopram
Medication error potential	None reported.
Contraindications and warnings	**Contraindications:** Hypersensitivity to doxapram or any component. Seizure disorders; possible pulmonary embolism; mechanical disorders of ventilation (e.g., mechanical obstruction, muscle paresis (including neuromuscular blockade), flail chest, pneumothorax, acute bronchial asthma, pulmonary fibrosis or other conditions resulting in restriction of chest wall, muscles of respiration or alveolar expansion); evidence of head injury, cerebral vascular accident, or cerebral edema; and significant cardiovascular disorders including those associated with hyperthyroidism.[1] **Warnings:** Avoid use in conjunction with mechanical ventilation. Doxapram contains benzyl alcohol. Large amounts of benzyl alcohol may cause a potentially fatal toxicity ("gasping syndrome") in neonates. (See Appendix C.)
Infusion-related cautions	Monitor blood pressure closely for evidence of hypertension.[1–3] Extravasation should be avoided because of the potential for thrombophlebitis or local skin irritation.[1]
Dosage	*Typically considered a third-line agent that should be reserved for neonates unresponsive to theophylline or caffeine. (See Additives section and Comments section.)* **Neonatal apnea:** Loading dose of 2.5–3 mg/kg[4,5] followed by continuous infusion of 0.2 mg/kg/hr.[2,4 6,7] Alternatively, a continuous infusion of 0.5 mg/kg/hr with increases of 0.5 mg/kg/hr up to a maximum of 2.5 mg/kg/hr for a total length of infusion of 48 hours.[6] Then decrease to lowest dose that controls apnea.[6] In one study, 0.2 mg/kg/hr was as effective as 1–2.5 mg/kg/hr when used with a methylxanthine.[4] **Neonatal extubation:** A small study in premature neonates began with an infusion of 0.5–1 mg/kg/hr and titrated to ≤2.5 mg/kg/hr for 48 hours.[7] In another larger study, 27 preterm infants who received an infusion of 3.5 mg/kg over 20 minutes followed by 1 mg/kg/hr for 48 hours after extubation had no greater likelihood of remaining extubated than the control group.[8] In addition, an intervention review concluded that the routine use of doxapram to facilitate extubation in preterm neonates was not warranted.[9] ***Adults* with postanesthesia respiratory depression, drug-induced respiratory depression, chronic obstructive pulmonary disease**[1]**:** 0.5–1 mg/kg q 5 min up to a maximum dose of 2 mg/kg. Alternatively, 5 mg/min until a satisfactory response is obtained and maintained at an infusion of 1–3 mg/min up to a total dose of 4 mg/kg (maximum 300 mg). The regimen may be repeated if relapse occurs.
Dosage adjustment in organ dysfunction	Use cautiously in significantly impaired renal or hepatic function.[1]
Maximum dosage	2.5 mg/kg/hr for 48 hours in neonates.[2,6,7,10] 3 g/day in *adults*.[1]
Additives	Contains benzyl alcohol 0.9% as a preservative.[1] (See Appendix C for specific information about benzyl alcohol toxicity.)
Suitable diluents	D5W, D10W, NS.[1]

Doxapram HCl

Maximum concentration	2 mg/mL.[1,11]
Preparation and delivery	**Compatibility:** Incompatible with alkaline solutions such as aminophylline, furosemide, sodium bicarbonate, and thiopental.[1,11]
IV push	Not recommended. Rapid infusion may result in hemolysis.[1]
Intermittent infusion	For loading dose dilute in D5W, D10W, or NS (1 mg/mL) and infuse no faster than 5 mg/min in *adults*.[1]
Continuous infusion	Continuous infusion may be used.[1]
Other routes of administration	Not indicated.[1]
Comments	**Adverse effects:** A group of preterm infants with mental delay was compared to a control group matched for gestational age, birth weight, sex, intraventricular hemorrhage grade, and socioeconomic status.[12] Steroid use and methylxanthine use was similar; however, both oxygen supplementation and doxapram therapy were longer in the group with mental delay compared to controls.[12] This led investigators to speculate about the possible role of benzyl alcohol. Subsequently, investigators evaluated 20 preterm neonates during escalating doxapram doses using cerebral Doppler ultrasonography and near-infrared spectroscopy.[13] Doxapram increased oxygen consumption and requirements and at the same time decreased oxygen delivery. Investigators proposed that these effects are caused by decreased cerebral blood flow. QTc interval prolongation has been reported in premature infants receiving 0.5–1 mg/kg/hr for 72 hours.[14] **Monitoring:** Heart rate, blood pressure, and deep tendon reflexes.[1]

Doxycycline Hyclate

Brand names	Vibramycin IV and generics
Medication error potential	USP reports confusion with Declomycin, dicloxacillin, dicyclomine, doxazosin, doxepin, minocycline, and tetracycline.[1]
Contraindications and warnings	**Contraindications:** Persons who have shown hypersensitivity to any of the tetracyclines.[2] **Warnings:** Use during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent tooth discoloration (yellow-gray-brown).[2,3] This is more common during long-term use but has been observed following repeated short-term courses.[2,3] Tetracycline drugs should not be used in this age group except when the benefit clearly outweighs this risk.[2–4] Tetracyclines may cause an increase in BUN; however, this does *not* occur with the use of doxycycline in patients with impaired renal function.[2]
Infusion-related cautions	Avoid extravasation.[5] (See Appendix E for treatment of extravasation.) Phlebitis occurs frequently.[6,7]
Dosage	**Children <8 years of age:** See Contraindications and Warnings section. **Children ≥8 years of age** **≤45 kg:** 2–4 mg/kg/day divided q 12–24 hr.[4] **>45 kg:** 100–200 mg/day divided q 12–24 hr.[4] **Pelvic inflammatory disease:** 200 mg/day divided q 12 hr.[4]
Dosage adjustment in organ dysfunction	One reference suggests doxycycline accumulates in chronic renal failure[8] and another suggests if CrCl <10 mL/min, the dose should be reduced to 2 mg/kg/day divided q 12 hr.[9] Others have found little to no accumulation.[10,11]
Maximum dosage	200 mg/day for children ≥8 years of age and >45 kg.[2,4]
Additives	100-mg vials contain 480 mg of ascorbic acid.[5] Mannitol is also present in some preparations.[5]
Suitable diluents	D5W, LR, NS, or R.[2,5]
Maximum concentration	1 mg/mL.[5] Concentrations <0.1 mg/mL are not recommended.[2] Phlebitis is more common when more concentrated solutions are administered.[6]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.[12] **Photosensitivity:** Protect from light exposure until ready to use. Cover during infusion is recommended if solution is exposed to sunlight.[5] Stable for 48 hours if exposed to fluorescent light only.[2]
IV push	Not recommended.[2,5]

Intermittent infusion	0.1–1 mg/mL[2,5] over 1–4 hours.[2,5] A recommended minimum infusion time for a dose of 100 mg (0.5 mg/mL) is 1 hour.[2]
Continuous infusion	Not given by this method.[2]
Other routes of administration	None.
Comments	**Rare adverse effects:** Nail discoloration has occurred in an 11-year-old receiving oral doxycycline 200 mg on day 1 followed by 100 mg daily for 10 days.[13] Doxycycline can form stable calcium complex in any bone-forming tissue. A temporary decrease in the fibula growth rate has been observed in premature neonates who receive tetracyclines.[2–4] **Osmolality:** 1 mg/mL in D5 and in NS was 292 mOsm/kg and 310 mOsm/kg, respectively.[5]

Droperidol

Brand names	Inapsine, generic
Medication error potential	Look-alike, sound-alike drug names. USP reports that Inapsine has been confused with Imitrex; no patient harm resulted.[1]
Contraindications and warnings	**U.S. boxed warning:** QT prolongation and torsades de pointes have been reported in patients treated with droperidol at or below recommended doses. Cases have occurred in patients with no known risk factors for QT prolongation and some have been fatal.[2] Droperidol should only be used in patients who fail to respond to other therapies and risks of administration must be weighed against any potential benefit.[2] Prior to administration, all patients should have a 12 lead ECG to assess for QT interval prolongation.[2] **Contraindications:** Contraindicated in those with known or suspected QT prolongation including those with congenital long QT syndrome.[2] Contraindicated in patients with known hypersensitivity to droperidol.[2] **Other warnings:** Droperidol should be administered cautiously in patients at risk for prolonged QT interval (congestive heart failure, cardiac hypertrophy, significant bradycardia, significant cardiac disease, low potassium or magnesium concentrations, concomitant drug therapy that prolongs the QT interval, concomitant Class I and III antiarrhythmics or monoamine oxidase inhibitors, concomitant diuretic use). Administer cautiously in patients >65 years of age and in those with alcohol abuse, benzodiazepine use, or opiate use.[2] Severe hypertension and tachycardia have been observed in patients with known or suspected pheochromocytoma.[2]
Infusion-related cautions	Fluids and other agents used to manage hypotension should be available when giving droperidol.[2] Elevated blood pressure has occurred when given concomitantly with fentanyl and other parenteral analgesics.[2]
Dosage	Not recommended for any use other than perioperative nausea and vomiting unresponsive to other therapies.[2] **Postoperative nausea/vomiting (2–12 years)** **Prophylaxis:** 0.01–0.015 mg/kg/dose administered near end of surgery, with a maximum dose of 1.25 mg.[3] Although some reports demonstrated up to 0.075 mg/kg/dose to be most effective,[4-11] due to side effects seen with higher doses, it is recommended to not exceed 0.05 mg/kg.[3] **Treatment:** 0.1 mg/kg/dose.[10] Administer additional doses with caution and only if benefit clearly outweighs risk.[2]
Dosage adjustment in organ dysfunction	Use cautiously in patients with impaired hepatic or renal function.[2]
Maximum dosage	Maximum initial dose is 0.1 mg/kg in children (2–12 years) and 2.5 mg/dose in *adults*.[2]
Additives	None.
Suitable diluents	D5W, LR, NS.[12]

Droperidol

Maximum concentration	2.5 mg/mL.[2,12]
Preparation and delivery	For PN compatibility information, please see Appendix D.
IV push	2.5 mg/mL given by slow IV injection, over 2–5 minutes.[2,12] (See Infusion-Related Cautions section.)
Intermittent infusion	No information is available to support administration by this method.
Continuous infusion	No information is available to support administration by this method.
Other routes of administration	Solutions of 2.5 mg/mL may be given IM.[2,12]
Comments	**Significant adverse effects:** Acute dystonia has been reported in two patients (ages 14 and 16 years) receiving droperidol (0.04 and 0.08 mg/kg) with patient-controlled analgesia.[13] **Drug interactions:** Droperidol should not be given concomitantly with other agents known to prolong the QT interval, agents that cause electrolyte imbalances, or CNS depressant agents.[2]

Edetate Calcium Disodium

Brand names

Edetate calcium disodium (calcium disodium versenate) has also been referred to as calcium EDTA (see Contraindications and Warnings section)

Medication error potential

Look-alike, sound-alike drug names.

ISMP and USP report that edetate calcium disodium (calcium EDTA) has been confused with edetate disodium (disodium EDTA); patient death resulted.[1,2]

Contraindications and warnings

U.S. boxed warning: Mortality from lead encephalopathy in pediatric patients has been high. Patients with lead encephalopathy and cerebral edema may experience a lethal increase in intracranial pressure following IV infusion. IM administration is the preferred route in these patients. When giving intravenously, avoid rapid infusion. Do not exceed the recommended daily dose.[3]

Other warnings: In January 2008, the FDA issued an advisory regarding patient deaths, including the death of at least one child (see Comments section), that have occurred when edetate disodium was mistakenly given instead of edetate calcium disodium.[4,5] Edetate disodium (disodium EDTA) should never be used to treat lead poisoning because it chelates calcium and induces tetany and potential fatal hypocalcemia.[6–8] Edetate disodium is no longer available in the United States.

Infusion-related cautions

Rapid infusion may result in thrombophlebitis or precipitation of encephalopathy.[3] Diluted solutions (≤5 mg/mL) infused over at least 4 hours may decrease the risk of thrombophlebitis.[9]

Dosage

Treatment of lead poisoning (dosing is based on blood lead concentration [BLC] and clinical presentation). Continuation of therapy should also be based on BLC. Patients who require >5 days of therapy should have a 2–4 day drug-free period between courses.[8–10]

Measure BLC 7–21 days after therapy to determine if retreatment is necessary.[8,9]

Combine with dimercaprol (British anti-Lewisite or BAL); second course may be required after 2–4 days; give third course if BLC ≥50 mcg/dL within 48 hours (wait 5–7 days before third course).[8–10]

Neonates: Two case reports describe treatment with edetate calcium disodium in newborns. A term gestation, 3-kg baby received a continuous confusion of 1000 mg/m^2/day beginning on 4th day of life (at the time of the second BAL injection) and continued for 3 days.[11] A term gestation, 3.7-kg newborn underwent exchange transfusion 12 hours after birth followed by BAL and continuous infusion edetate calcium disodium 50 mg/kg/day initiated at 36 hours of life and continued for 5 days.[12]

Acute lead encephalopathy: 1500 mg/m^2/day for 5 days.[8,10] IM administration is the preferred route in patients with lead encephalopathy and cerebral edema.[3] (See Contraindications and Warnings section.)

Symptomatic and/or BLC ≥70 mcg/dL (symptomatic or asymptomatic): 1500 mg/m^2/day[8] or 50 mg/kg/day[9] for 5 days via an infusion over 8–24 hours.[3,8–10] One reference recommends 1000 mg/m^2/day if BLC ≥70 mcg/dL and patient is asymptomatic.[10]

Combination therapy with BAL until BLC is ≤50 mcg/dL.[10] Second and third courses may be given depending on BLC and severity of symptoms.[3,8–10]

BLC of 45–69 mcg/dL (asymptomatic): 1000 mg/m^2/day[8,10] or 25 mg/kg/day[9] for 5 days via an infusion over 8–24 hours[3,8–10] or in divided doses q 8–24 hr (IV/IM)[10]; a second course may be required if BLC rebounds.[8]

Edetate Calcium Disodium

Dosage *(cont.)*	**BLC 25–44 mcg/dL:** Chelation therapy not routinely given.[8,9] **Provocative chelation test:** *No longer recommended by the AAP.*[9] After patient empties bladder, infuse 500 mg/m^2 in D5W over 1 hour[8,10,13] and collect urine for the following 8 hours. Dose may also be given IM. Urinary excretion ≥200 mcg of lead or a ratio of urinary lead (mcg) to edetate calcium disodium dose (mg) of ≥0.6 (children <36 months) or ≥0.7 (children >36 months) identifies patients who will respond to chelation therapy.[8,10,14] A 5-hour lead mobilization test has also been validated.[15] With IM therapy, infusing IV fluids after administration ensures a greater diuresis.[16]
Dosage adjustment in organ dysfunction	Reduce dose with pre-existing renal disease.[3] Stop therapy if anuria or severe oliguria develops.[3] Avoid in patients with inadequate urine flow.[8,10] **Dosing suggestions for *adults* with lead nephropathy**[3] **SCr 2–3 mg/dL:** 500 mg/m^2/dose q 24 hr for 5 doses. **SCr 3–4 mg/dL:** 500 mg/m^2/dose q 48 hr for 3 doses. **SCr >4 mg/dL:** 500 mg/m^2/dose once weekly. These regimens may be repeated monthly if needed.
Maximum dosage	75 mg/kg/day (reserved for severely symptomatic patients) not to exceed 1 g/24 hr.[17] Five times the recommended dose was infused over 24 hours in a 16-month-old without adverse effects.[3]
Additives	Contains 5.3 mEq sodium/g of edetate calcium disodium.[18]
Suitable diluents	NS, D5W.[8,18]
Maximum concentration	0.5% or 5 mg/mL.[8–10,18]
Preparation and delivery	Supplied from the manufacturer as a solution of 200 mg/mL; must be diluted prior to administration.[3,18]
IV push	Not recommended.[3,9,18]
Intermittent infusion	Dilute to a concentration of <0.5%[8] or 2–4 mg/mL.[18] Although infusions of 15–60 minutes have been used,[8,10] 4 hours or greater is recommended[9] and usually given over 8–12 hours; however, continuous infusion is preferred.[8,9]
Continuous infusion	Preferred method of administration in hospitalized patients.[8,10] Dilute to a concentration of <0.5%[8] or 2–4 mg/mL.[18]
Other routes of administration	IM administration is extremely painful; must be given with procaine or lidocaine (final anesthetic concentration = 0.5%) at intervals of 8–12 hours.[3,10,18]

Edetate Calcium Disodium

Comments

Significant adverse effects: Renal toxicity is dose-related and reversible, and it rarely occurs at daily doses $<$1500 mg/m^2 if the patient is adequately hydrated.[3,8,10] Edetate calcium disodium is renally excreted; adequate hydration and urine output must be maintained to reduce nephrotoxicity.[3,8–10] Beginning 1–2 days after 5 days of edetate calcium disodium and BAL therapy, about 16% of children developed increased SCr lasting for $\leq$22 days and oliguria lasting for 2–4 days.[19]

Hypercalcemia has been reported following treatment with edetate calcium disodium.[3]

Laboratory interference: A falsely elevated lead concentration may occur if blood is drawn during a continuous infusion of edetate calcium disodium; therefore, the infusion should be stopped at least 1 hour before a test is performed.[20]

Other: Animal studies found a redistribution of lead from bone to target organs (e.g., brain and kidneys) following edetate calcium disodium administration.[21]

Neonatal lead poisoning has been treated with edetate calcium disodium in combination with BAL, with and without exchange transfusion within the first week of life.[11,12]

A 5-year-old autistic child died from cardiac arrest due to hypocalcemia during his third chelation treatment when edetate disodium was given instead of edetate calcium disodium.[5]

Edrophonium Chloride

Brand names	Enlon, Tensilon
Medication error potential	Look-alike, sound-alike drug names. USP reports that Tensilon has been confused with tamsulosin; no patient harm resulted.[1]
Contraindications and warnings	**Contraindications:** Edrophonium is contraindicated in patients with known hypersensitivity to anticholinesterase agents and in patients with mechanical intestinal or urinary obstructions.[2] **Warnings:** Use with caution in patients with asthma or with cardiac dysrhythmias or cardiovascular disease (especially in those taking digoxin).[2,3]
Infusion-related cautions	Hypersensitivity, arrhythmias, bronchospasm, and laryngospasm have been reported.[2,3] Rare cases of cardiac and respiratory arrest have occurred with edrophonium administration.[2] Atropine sulfate injection should be available to reverse signs and symptoms of life-threatening cholinergic reaction.[2,3]
Dosage	**Anti-arrhythmic:** Edrophonium has been used to terminate supraventricular tachycardia but has generally been replaced by other antiarrhythmic agents.[4] **Myasthenia gravis (diagnosis):** Edrophonium establishes the diagnosis in 90% to 95% of patients suspected of having the disease.[4] If a cholinergic reaction occurs after the initial dose, the test should be discontinued.[2] **Infants:** Manufacturer recommends a dose of 0.5 mg.[2] Another reference recommends 0.04 mg/kg over 1 minute followed by 0.16 mg/kg (max 10 mg) if no response.[5] **Children:** Initial dose of 1 mg (≤34 kg) or 2 mg (>34 kg) over 1 minute. If no response within 45 seconds, repeat dose q 30–45 sec up to a maximum cumulative dose of 5 mg for children ≤34 kg and up to 10 mg for heavier children and adolescents.[2,3] Alternatively, some recommend that children receive a total of 0.2 mg/kg or 6 mg/m^2. One-fifth of the dose should be given over 1 minute. If no response occurs in 45 seconds, the remainder should be given.[4] **Myasthenia gravis (assessment of anticholinesterase therapy):** Edrophonium is used to determine the adequacy of chronic dosing of another anticholinesterase medication in a patient with myasthenia gravis. 0.04 mg/kg (up to 1–2 mg) given 1 hour after administration of the oral drug being used to chronically treat myasthenia gravis.[2,3] If the patient's muscle strength or forced vital capacity improves following edrophonium, the dose of the chronic therapy should be increased.[5,6] If cholinergic symptoms appear, the dose of chronic therapy should be decreased.[2,3] Because it requires several days for results to occur following changes in chronic oral dosage, the patient should be tested with edrophonium every 1–3 days after dosage adjustment of the chronic medication.[4] **Postsurgical reversal of nondepolarizing neuromuscular blocking agents:** 0.4–1 mg/kg administered IV over 30–45 seconds and repeated q 5–10 min as needed, up to a maximum of 40 mg total.[2,6–8] If a larger dose of edrophonium is required (≥0.5 mg/kg), it should be preceded by IV atropine sulfate (0.01 mg/kg; minimum 0.1 mg and maximum 2 mg).[5,7,8]
Dosage adjustment in organ dysfunction	Dose may need to be reduced in patients with chronic renal failure.[3]

Edrophonium Chloride

Maximum dosage	Maximum cumulative dose when used for diagnostic testing for myasthenia gravis is 5 mg for children ≤34 kg and up to 10 mg for heavier children and *adults*.[2] Maximum cumulative dose when used to reverse effects of a neuromuscular blocking agent is 40 mg.[2]
Additives	Contains 0.2% sodium sulfite and 0.45% phenol.[2] (See Appendix C for more specific information about potential adverse effects of sulfites.)
Suitable diluents	Not diluted prior to administration.[2]
Maximum concentration	10 mg/mL.[2,9]
Preparation and delivery	No specific comments; see product labeling.
IV push	10 mg/mL given over 1 minute.[2]
Intermittent infusion	Not recommended.
Continuous infusion	Not recommended.
Other routes of administration	Edrophonium is usually given IV but may also be given IM or SC.[2,3] For the diagnosis of myasthenia gravis, the following doses are recommended for IM administration: **Infants:** 0.5–1 mg IM. **Children** **≤34 kg:** 2 mg IM. **>34 kg:** 5 mg IM. There is a delay of 2–10 minutes before a reaction is noted following IM administration.[2]
Comments	**Drug interactions:** Administration of edrophonium may prolong the effect of succinylcholine.[3] **Other:** While edrophonium reverses the effects of most nondepolarizing neuromuscular blocking agents, it is less effective in reversing depolarizing agents such as mivacurium, decamethonium, and succinylcholine.[2,8]

Enalaprilat

Brand names	Vasotec IV and generics
Medication error potential	Enalapril maleate (oral form) and enalaprilat base (injectable form) are not identical and dosage is expressed in terms of the salt form. Care should be taken in conversion from IV to oral dosing or vice versa.[1,2]
Contraindications and warnings	**U.S. boxed warning:** May cause injury and death to the developing fetus when used during pregnancy.[3] **Contraindications:** Patients with known hypersensitivity to any component of this product, those with a history of angioedema due to previous treatment with an angiotensin converting enzyme inhibitor, and individuals with hereditary or idiopathic angioedema.[3,4] (See Comments section.) **Other warnings:** Anaphylactoid reactions and angioedema with laryngeal edema have occurred.[3] Immediate airway management and treatment with epinephrine solution 1:1000 (0.3–0.5 mL), oxygen, and IV steroids may be required. (See Comments section.)
Infusion-related cautions	Monitor for hypotension, especially in volume-depleted patients for 1–3 hours after the first dose or following an increase in dosage.[3]
Dosage	Should consider smaller dosage in patients receiving concomitant diuretics or in those with hyponatremia, hypovolemia, left ventricular outflow obstruction, or severe congestive heart failure.[3] **Hypertensive or congestive heart failure (left-right ventricular shunt)** **Neonates:** 5–10 mcg/kg/dose,[5] 5–30 mcg/kg/day divided q 8–24 hr.[6–8] Doses as large as 120 mcg/kg/day divided q 6 hr have been used.[9] Premature infants may require extended dosing intervals due to decreased GFRs.[6] **Infants and children:** 5–10 mcg/kg/dose up to 1.25 mg/dose.[10–15] Clinical response should occur in <15 minutes with peak effect after first dose occurring by 4 hours.[3] Therapy should be titrated according to blood pressure. **Adolescents and *adults:*** 1.25 mg/dose repeated q 6 hr as doses as large as 5 mg/dose q 6 hr have been tolerated.[3] Patients receiving a diuretic or those with hypotension should initially be given 0.625 mg. If inadequate response after 1 hour, give another 0.625 mg.
Dosage adjustment in organ dysfunction	Administer 75% of a dose when CrCl is 10–50 mL/min/1.73 m^2 and 50% of a dose if CrCl is <10 mL/min/1.73 m^2 in children.[16] Initial doses of *adults* with CrCl ≤30 mL/min/1.73 m^2 (SCr ≥3 mg/dL) is 0.625 mg.[3] Patients on dialysis have significant risk for excessive hypotension and should be monitored carefully.[16]
Maximum dosage	120 mcg/kg/day divided q 6 hr[5] or 150 mcg/kg/day divided q 8 hr.[5] In hypertensive emergencies, 320 mcg/kg q 6 hr have been used.[6] Although 20 mg/day divided q 6 hr have been tolerated in *adults,*[3,10,11,15,17] no data have clearly demonstrated these large doses are more effective in treating hypertension than 1.25 mg q 6 hr.
Additives	0.9% benzyl alcohol.[3] (See Appendix C for specific information about toxicity.)
Suitable diluents	D5LR, D5NS, D5W, Normosol R, NS.[3,17]

Enalaprilat

Maximum concentration	1.25 mg/mL (commercially available) provided the dose can be accurately measured.[3]
Preparation and delivery	**Stability:** Store below 30°C.[17] Stable for 24 hours once reconstituted.[17] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Not recommended.[3] However, an infusion over 60 seconds has been given without adverse effects.[6,12,13]
Intermittent infusion	Over 5 minutes.[3] If the patient is at risk for hypotension infuse over 1 hour.[3]
Continuous infusion	No reports of administration via this method.[3]
Other routes of administration	No reports of administration by other routes.[3]
Comments	**Rare adverse effects:** Angioedema generally occurs after the first dose but may also present at any time during therapy.[3] Edema may occur in the head, neck, extremities, or intestines; angioedema of the larynx, glottis, or tongue may cause airway obstruction that constitutes a medical emergency.[3] Transient hyperkalemia (>5.7 mEq/L) was reported in about 1% of hypertensive *adults* in clinical trials.[3] In most cases hyperkalemia resolved despite continued therapy. **Pharmacokinetics:** Neonates have decreased elimination and extended duration of action; hence, they may experience prolonged hypotension and acute renal failure.[6,10] **Drug interactions:** A variety of drug interactions have been reported. Consult appropriate resources for dosing recommendations before combining any drug with enalaprilat.

Enoxaparin Sodium

Brand names	Lovenox
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP reports that Lovenox has been confused with Levemir.[2] USP reports that enoxaparin has been confused with dalteparin and Fragmin, and no patient harm occurred. Enoxaparin has been confused with Fluvoxamine and patient harm occurred. Lovenox has been confused with Lanoxin, Lasix, Levaquin, and Lovastatin, and no patient harm occurred. Lovenox has been confused with Luvox and patient harm occurred.[3]
Contraindications and warnings	**U.S. boxed warning:** Patients receiving enoxaparin who undergo spinal/epidural anesthesia are at increased risk for the development of an epidural or spinal hematoma.[4] **Contraindications:** Major bleeding, thrombocytopenia with positive in vitro antiplatelet antibodies, hypersensitivity to enoxaparin or any component, or hypersensitivity to porcine products, heparin, or benzyl alcohol.[4]
Infusion-related cautions	None noted.
Dosage	**Dosing adjustment for obesity:** Doses should be based on total body weight (TBW).[5] In three morbidly obese children, prophylaxis doses of 0.14–0.49 mg/kg (40–100 mg) q 12 hr were required to achieve anti-Xa values of 0.1–0.3 unit/mL.[6] In morbidly obese, critically ill *adults,* a prophylaxis regimen of 0.5 mg/kg SC q 12 hr satisfactorily achieved goal anti-Xa (in this study, goal was 0.2–0.5 unit/mL 4 hr after 3rd or 4th dose).[7] In both studies, higher doses were required compared to typical *adult* cutoffs (e.g., 40 mg q 24 hr). Anti-Xa levels correlate with dosing based on TBW in *adults* weighing up to 144 kg.[8] **Prophylaxis[9]:** Target anti-factor Xa (anti-Xa) concentrations for prophylaxis range from 0.1–0.3 units/mL.[9] **<2 months of age:** 0.75 mg/kg SC q 12 hr. **>2 months of age:** 0.5 mg/kg SC q 12 hr. **Treatment[9–14]:** Target anti-Xa concentrations for treatment (once- or twice-daily dosing regimens) range from 0.5–1 unit/mL when obtained 4–6 hours after a dose, or 0.5–0.8 unit/mL at 2–6 hours after a dose.[9] **<2 months of age:** 1.5 mg/kg SC q 12 hr. **>2 months of age:** 1 mg/kg SC q 12 hr. Compared to infants ≥37 weeks gestational age (WGA), those <37 WGA required larger doses both to achieve (1.9 ± 0.6 mg/kg versus 1.6 ± 0.3 mg/kg q 12 hr) and to maintain (2.1 ± 0.6 mg/kg versus 1.7 ± 0.3 q 12 hr) target anti-Xa concentrations.[15] Similarly, 10 preterm infants with thromboses (24–34 WGA) required an average dose of 2.27 mg/kg (2–3.5 mg/kg) q 12 hr to maintain target anti-Xa concentrations; target anti-Xa was achieved at mean of 33 days of treatment (14–63 days).[16] Twenty-six neonates 23–41 WGA) being treated for venous thromboembolism (VTE) required 2.1 ± 0.6 mg/kg q 12 hr to achieve target anti-Xa levels; target levels were only achieved 40% of the time.[17] Doses from 0.94–2.36 mg/kg (mean 1.69 mg/kg) q 12 hr in infants ≤2 months old and from 0.56–1.6 mg/kg (mean 1.06 mg/kg) q 12 hr in patients >2 months old were needed to achieve therapeutic anti-Xa concentrations.[13] Still another study reported that 12 preterm infants <2 months old required 1.94 ± 0.39 mg/kg q 12 hr to achieve therapeutic concentrations compared to term infants who achieved therapeutic concentrations with 1.65 ± 0.14 mg/kg q 12 hr.[18]

Dosage *(cont.)*

Thus, infants <2 months old may require larger doses than are currently recommended.[19]

Cardiac ICU: Infants and children in a cardiac ICU required doses that were a median of 50% above usual recommended doses for both prophylaxis and treatment. Mean dose required in infants <2 months of age for prophylaxis was 1.87 mg/kg q 12 hr and for treatment was 2.37 mg/kg q 12 hr. Mean dose required for patients >2 months was 1.06 mg/kg q 12 hr for prophylaxis and 1.82 mg/kg q 12 hr for treatment.[20]

Once-daily dosing has been studied. For treatment of venous thromboembolism, patients received standard doses for 10–14 days (q 12 hr regimen), followed by either a twice-daily or a once-daily regimen. Patients in the once-daily regimen group received the following: if <1 year old, 1.5 mg/kg q 24 hr; if >1 year old, 1 mg/kg q 24 hr. Goal peak anti-Xa was 0.8 unit/mL at 2–4 hours after dose.[21] Another (pilot) study reported a similar regimen in patients >3 months old with deep vein thrombosis (DVT). Patients received twice-daily dosing during the initial treatment period (7–14 days) but then could receive 1.5 mg/kg q 24 hr or 1 mg/kg q 12 hr. No differences in safety or efficacy were found between the two regimens.[22]

Concentrations should be drawn 4–6 hours after a SC dose. The following recommendations are made for dosage adjustment[23,24]:

Anti-Xa (units/mL)	<0.35	0.35–0.49	0.5–1	1.1–1.5	1.6–2	>2
Dose adjust	Increase dose 25%	Increase dose 10%	No change	Decrease dose 20%	Decrease dose 30%	Decrease dose 40%
Redose	On time	On time	On time	On time	Delay dose 3 hr	Delay dose until anti-Xa <0.5
Measure anti-Xa	4 hr after next dose	4 hr after next dose	Every other day	4 hr after next dose	4 hr after next dose	q 12 hr until <0.5

Dosing in *adults*[4]

Abdominal surgery or medical patients requiring venous thromboembolism (VTE) prophylaxis: 40 mg SC once daily.

Hip or knee replacement surgery prophylaxis: 30 mg SC q 12 hr.

Unstable angina or non-Q-wave myocardial infarction: 1 mg/kg SC q 12 hr.

Treatment of acute ST-segment elevation myocardial infarction: 30 mg IV bolus plus 1 mg/kg SC followed by 1 mg/kg SC q 12 hr. Refer to package insert for detailed information about timing of doses.

Treatment of DVT with or without pulmonary embolism: 1 mg/kg SC q 12 hr or 1.5 mg/kg SC once daily.

Dosage adjustment in organ dysfunction

If CrCl is 10–29 mL/min/1.73 m^2, give 70% of usual dose; if CrCl <10 mL/min/1.73 m^2, give 50% of usual dose q 24 hr. For patients receiving intermittent hemodialysis or peritoneal dialysis, give 50% of usual dose. For patients receiving continuous renal replacement therapy, give 70% of usual dose and monitor anti-Xa levels.[25] In *adults* with CrCl <30 mL/min who require a prophylaxis regimen, decrease dose to 30 mg SC once daily. For *adults* with CrCl <30 mL/min requiring treatment of acute ST-segment elevation myocardial infarction and are <75 years old, in conjunction with aspirin give an IV bolus of 30 mg plus 1 mg/kg SC followed by 1 mg/kg SC once daily. For all other *adults* with CrCl <30 mL/min requiring a treatment regimen, give 1 mg/kg SC once daily.[4]

Use caution in patients with hepatic failure.[4,15,26]

Standard doses may produce variable anti-Xa results and require adjustments more frequently in patients with cardiac conditions.[26]

Enoxaparin Sodium

Maximum dosage	1.5 mg/kg in *adults*.[4] One group reported that 3.5 mg/kg q 12 hr was required to produce therapeutic anti-Xa concentrations in a preterm neonate.[16]
Additives	Prefilled syringes and graduated prefilled syringes are preservative-free.[4] Each multiple-dose vial (300 mg/mL) contains benzyl alcohol 15 mg/mL.[4] (See Appendix C for specific information about benzyl alcohol toxicity in neonates.)
Suitable diluents	May be mixed with D5W or NS for IV administration.[27]
Maximum concentration	150 mg/mL (commercially available).[4]
Preparation and delivery	A tuberculin syringe or equivalent should be used for administration.[4]
IV push	Not indicated. IV bolus dosing has been reported.[28] (See Comments section.)
Intermittent infusion	Not indicated.
Continuous infusion	Not indicated.
Other routes of administration	Administered SC, not IM.[4] (See Comments section.)
Comments	Enoxaparin diluted to 20 mg/mL with preservative-free SW did not lose significant anticoagulant activity for 4 weeks.[29] **Pharmacokinetics and pharmacodynamics/IV administration:** Seven infants and children in a pediatric ICU (age 2 months to 3 years) received enoxaparin IV every 8 or 12 hours. The therapeutic dose for those $<$1 year was 2.4 ± 0.58 mg/kg/dose and for those $\geq$1 year it was 1.11 ± 0.13 mg/kg/dose. Most patients had subtherapeutic anti-Xa levels by 6–8 hours after a dose, suggesting the need for more frequent (i.e., q 8 hr) dosing.[28] One 29-WGA preterm infant (normal cranial ultrasound) with a suspected radial artery thrombus and discolored fingers was given 1 mg/kg IV q 8 hr for 7 days. Perfusion improved and only the tip of one finger was ultimately affected.There was no bleeding associated and no future thromboses were noted.[30] **Adverse effects:** Enoxaparin has been associated with the development of heparin-induced thrombocytopenia in a pediatric patient.[31] **Monitoring:** CBC including platelet count during treatment. Anti-Xa concentrations should be measured 4–6 hours after a dose.[4]

EPINEPHrine HCl

Brand names

Adrenalin, EpiPen, EpiPen Jr, Twinject, generic

Medication error potential

ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1]

Look-alike, sound-alike drug names.

ISMP and USP report that EPINEPHrine has been confused with ePHEDrine.[2,3] The USP also reports that EPINEPHrine has been confused with Neo-Synephrine, norepinephrine, and phenylephrine. Adrenalin has been confused with ePHEDrine.[3]

EPINEPHrine is available in two concentrations (1:1000 or 1-mg/mL dilution and 1:10,000 or 0.1-mg/mL dilution).[4] Choose products carefully. (See Dosage section.)

Contraindications and warnings

Contraindications: No absolute contraindications exist in a life-threatening situation.[5] Otherwise, contraindications include presence of cardiac dilatation or coronary insufficiency, organic brain damage, patients receiving halogenated hydrocarbon or cyclopropane anesthetics,[4] and narrow angle glaucoma.[6]

Warnings: Use with caution, if at all, in patients with cardiovascular disease, hypertension, diabetes, and hyperthyroidism.[4,6]

Overdose may result in cerebrovascular hemorrhage.[6]

Infusion-related cautions

Bradycardia, tachycardia, dysrhythmias, myocardial ischemia, syncope, weakness, renal failure, and hypertension have occurred.[7–10]

Extravasation may cause local ischemia and tissue necrosis.[11–13] Therefore, infusion should be via a secure peripheral catheter or, preferably, a central route.[10,14] To prevent necrosis, aliquots of phentolamine mesylate (0.1–0.2 mg/kg up to 10 mg in 10 mL NS) should be injected intradermally into the ischemic area.[13] IO infusion may be used while attaining central access.[14]

A series of case reports on a 13-year-old child, a 31-year-old *adult*, and a 39-year-old *adult* who accidentally discharged an EPINEPHrine autoinjector into their thumbs reported that local injection of 1 or 3 mL of SC terbutaline (1 mg in 10 mL NS) was an effective alternative to phentolamine.[15]

See Appendix E for additional information regarding extravasation treatment.

Dosage

The restoration of intravascular volume should be addressed if hypovolemia occurs during treatment.[4]

CPR

Asystole/bradycardia

Neonates: 0.01–0.03 mg/kg (0.1–0.3 mL/kg of 1:10,000 dilution) IV[16,17] (preferred) or IO.[13] Repeat every 3–5 minutes PRN.[10]

Alternatively, 0.05–0.1 mg/kg (0.5–1 mL/kg of 1:10,000 dilution or 0.05–0.1 mL/kg of 1:1000 dilution) ET followed by 1 mL NS until IV or IO access established.[16,17] Repeat every 3–5 minutes PRN.[10]

Infants and children: 0.01 mg/kg (0.1 mL/kg of 1:10,000 dilution,[4] maximum of 1 mg/dose) given IV or IO. Repeat every 3–5 minutes PRN.[10,13]

Alternatively, 0.1 mg/kg (0.1 mL/kg of the 1:1000 dilution, maximum of 2.5[10]–10 mg/dose) ET followed by 1–5 mL NS.[10,13]

Dosage *(cont.)*

See Comments section regarding high-dose EPINEPHrine IV.

Persistent shock after volume resuscitation: 0.1 mcg/kg/min increased by 0.1 mcg/kg/min to desired response. Usual dose range 0.1–1 mcg/kg/min IV or IO,[10] up to 5 mcg/kg/min in children,[13] and 1 mcg/kg/min in neonates.[17]

Toxins/overdose (e.g., beta blockers, calcium channel blockers, tricyclic antidepressants)[10]: 0.01 mg/kg (0.1 mL/kg of 1:10,000 dilution) up to 1 mg given IV or IO. If no response, may give higher doses up to 0.1 mg/kg (0.1 mL/kg of 1:1000 dilution) IV or IO.[18] Alternately, may infuse 0.1–1 mcg/kg/min; consider higher doses in the case of refractory hypotension.[10]

Anaphylaxis

Mild symptoms (e.g., pruritus, erythema, urticaria, angioedema): 0.01 mg/kg (0.01 mL/kg of the 1:1000 dilution, maximum of 0.3–0.5 mg/dose) given IM[9,12]; may be repeated q 5–20 min[13,18] for up to 3 doses if symptoms continue or recur.[19] SC administration is no longer recommended as higher concentrations are more rapidly achieved with IM administration.[19] If anaphylaxis was caused by an agent that was injected, EPINEPHrine can be injected into the same site to minimize absorption.[19]

Life-threatening symptoms (e.g., severe bronchospasm, laryngeal edema, other airway compromise, shock, cardiovascular collapse): See CPR in the Dosage section.[10,13,18] Continuous infusion should be started if repeated doses are required.[10,13,18] Infusions as high as 1.5 mcg/kg/min may be required.[19]

Patients previously on beta-adrenergic blocking agents may be less responsive to EPINEPHrine and may require more aggressive therapy.[19] Likewise, some anaphylactic reactions (e.g., latex allergy) require large doses.[13]

Asthma: *The National Asthma Education and Prevention Program Expert Panel Report 3* states that there is no proven advantage of systemic beta-agonist therapy over aerosol.[20] However, a dose of 0.01 mg/kg (0.01 mL/kg of 1:1000 dilution, maximum of 0.3–0.5 mg) SC q 20 min for 3 doses may be used.[13,20]

Dosage adjustment in organ dysfunction

No dosage adjustment required in renal dysfunction.[21]

Maximum dosage

See Dosage section above for maximum dosages based on indication, patient age, and route.

Additives

Some products contain bisulfite and sodium chloride,[4] whereas others are preservative free.[22] Some products may also contain chlorobutanol.[6] (See Appendix C for more specific information about potential adverse effects of sulfites.)

Suitable diluents

D–LR, D–S, D5LR, D5NS, D5W, D10W, LR, NS. Not compatible with alkaline or oxidizing solutions such as sodium bicarbonate and nitrites.[23]

Maximum concentration

0.1 mg/mL (1:10,000 dilution) for IV push and IO administration or 1 mg/mL (1:1000 dilution) for ET administration and IV/IO in select cases of overdose.[10,13] EpiPen Jr delivers a dose of 0.15 mg in a concentration of 0.5 mg/mL (1:2000 dilution) and EpiPen delivers a dose of 0.3 mg in a concentration of 1 mg/mL (1:1000 dilution).[5] For continuous infusion, 64 mcg/mL has been reported as a maximum.[24]

EPINEPHrine HCl

Preparation and delivery	**Preparation:** Hemodynamic instability may be attributed to significant variability between the ordered dosage and the actual solution concentration of EPINEPHrine. Failure to consider the HCl salt in the stock drug accounted for some, but not all, of the inaccuracy in preparation.[25] **Stability/photosensitivity:** EPINEPHrine is easily destroyed by oxidants and in alkaline solutions; therefore, solutions should be protected from light. Do not infuse if solution is pinkish, darker than slightly yellow, or if it contains a precipitate.[23] **Compatibility:** For PN compatibility information, please see Appendix D. **Other:** For EPINEPHrine, the ET dose is up to 10 times the IV dose. The dose should be administered with or diluted in 1–5 mL NS, depending on patient size, and followed by manual ventilations.[10,13]
IV push	0.1 mg/mL (1:10,000 dilution) over seconds.[10,13]
Intermittent infusion	Not indicated.
Continuous infusion	1–64 mcg/mL. (See Dosage section; see Maximum Dosage section.) The Joint Commission recommends the use of standardized concentrations of vasoactive medications.[26] The ISMP and Vermont Oxford Network recommend a standard concentration of 10 mcg/mL for neonates.[27]
Other routes of administration	In pediatric emergencies, vascular (e.g., IV or IO) administration is preferred. ET administration is an alternative if vascular access is not obtained.[10,13,18] In anaphylaxis, the IM route is preferred, while SC is an alternative. In children, the IM dose should be injected into the anterolateral aspect of the thigh[18]; administration in the buttock should be avoided.[22] The SC route has been used in asthma.[10,18] EPINEPHrine may be given via intracardiac administration.[4]
Comments	High-dose EPINEPHrine IV (0.1–0.2 mg/kg) is no longer recommended in resuscitation[13] and may be harmful,[16] particularly in asphyxia.[10,28–32] High-dose EPINEPHrine may be considered in special circumstances such as beta-blocker overdose.[10,13,29] **Monitoring:** Blood pressure, heart rate, and ECG monitoring should occur continuously throughout therapy.[10] **Drug interactions:** Effects may be increased with other sympathomimetics (i.e., isoproterenol), tricyclic antidepressants, certain antihistamines (e.g., diphenhydramine, chlorpheniramine), sodium I-thyroxine, and monoamine oxidase inhibitors.[4,6]

Epoetin Alfa

Brand names	Epogen, Procrit
Medication error potential	Look-alike, sound-alike drug names. USP reports that Epogen has been confused with Neupogen; no patient harm resulted.[1]
Contraindications and warnings	**U.S. boxed warning:** Erythropoiesis-stimulating agents (ESAs) carry boxed warnings for increased mortality, serious cardiovascular and thromboembolic events, and increased risk of tumor progression or recurrence. In patients with renal failure, ESAs should be given to achieve and maintain hemoglobin (Hb) concentrations of 10–12 g/dL, as increased mortality and serious cardiovascular events have occurred in two clinical trials when targeting higher Hb concentrations (i.e., 13–14 g/dL).[2] The use of ESAs shortened survival and/or increased tumor progression in clinical cancer trials (breast, head and neck, lymphoid, non-small-cell lung, and cervical cancer). Use the lowest dose possible to avoid transfusions, use only for anemia in combination with chemotherapy, and discontinue when chemotherapy is completed. Erythropoiesis-stimulating agents should not be given to patients on myelosuppressive therapy if the anticipated outcome is cure.[2] Due to increased thrombotic events in patients receiving epoetin, deep vein thrombosis prophylaxis should be considered in any patients receiving epoetin and undergoing surgery.[2] **Contraindications:** Uncontrolled hypertension and known hypersensitivity to mammalian cell-derived products, and known hypersensitivity to albumin.[2] **Other warnings:** Hypertension and seizures have occurred in patients with chronic renal failure receiving epoetin. Pure red cell aplasia and severe anemia have also occurred. Withhold ESA therapy in any patient with antibody-mediated anemia.[2]
Infusion-related cautions	Do not administer through same IV line as other drugs.[3]
Dosage	To ensure the erythropoietic response, iron status should be evaluated and supplemental iron prescribed if stores are low. Transferrin saturation should be ≥20% and ferritin should be ≥100 ng/mL.[2] **Anemias (a target Hb) of 12 g/dL is usual)** **End-stage renal disease:** 10–150 units/kg 3 times weekly after dialysis through venous line in patients on hemodialysis.[4-9] In patients receiving continuous ambulatory or cycling peritoneal dialysis, SC injection is preferred, but 300 units/kg IV once a week have been used.[10] **HIV-infected children, zidovudine-treated:** 50–400 units/kg/dose 2–3 times weekly have been used. A dose of 40 and 90 units/kg 3 times weekly for 1 and 1.5 months were used in a 4- and 14-year-old child. Failure of adequate response in the 4-year-old child was attributed to use of a low dose for a short length of time.[11] Withhold dose if Hb exceeds 12 g/dL; may resume treatment with a 25% dose reduction once Hb <11 g/dL. **Children on chemotherapy:** In children 5–18 years of age, an initial dose of 600 units/kg IV (maximum 40,000 units) weekly for 16 weeks has been used.[12,13] If Hb did not increase by 1 g/dL after 4–5 weeks, the dose was increased to 900 units/kg (maximum 60,000 units). Sixty percent of patients required the increased dose.[12] In 37 children (1–18 years) with solid tumors, 300 units/kg was given IV or SC 3 times weekly if the Hb was <12 g/dL, and 150 units/kg was given 3 times weekly if the Hb was ≥12 g/dL and ≤16 g/dL.[14] Epoetin was not given if the Hb was ≥16 g/dL.[14] 450 units/kg SC given once weekly for 12 weeks has also been studied.[15]

Dosage *(cont.)*	**Prematurity:** 100–400 units/kg either 2–3 times a week up to 10 weeks,[16–21] daily for 10–14 days,[22–24] or 5 times a week for 2 weeks.[25] Generally, the initiation of treatment varies from within 72 hours of life to 5 weeks of age. **Epidermolysis bullosa:** 150 or 350 units/kg 3 times a week.[26] Adjust dosage monthly to use lowest dose sufficient to reduce RBC transfusions. If Hb has increased by <1 g/dL during initial 4 weeks of therapy (with adequate iron stores), then increase dose by 25% every 4 weeks until at target Hb. If the Hb increases by >1 g/dL in 2 weeks or the Hb reaches a concentration that will avoid transfusion, then decrease dose by 25%.[2,27] **Preoperative surgery (to reduce the need for blood transfusion):** In cardiac surgery, 150 or 300 units/kg given 2–3 times approximately 1 week prior to surgery and postoperatively for 2 doses or until the hematocrit is increased to the preoperative value.[28,29] In infants undergoing elective cranial vault remodeling, 600 units/kg SC given at 3 weeks, 2 weeks, and 1 week prior to surgery, combined with the use of recycled blood with "cell saver" technology, decreased transfusion requirements compared to control infants.[30]
Dosage adjustment in organ dysfunction	No dosage adjustment required.[2]
Maximum dosage	Not established. 900 units/kg/week have been given to children with cancer.[2] Doses of 1200[17] and 5000[31] units/kg/week have been given to neonates.
Additives	1-mL single-use (preservative-free) vials also contain 2.5 mg human albumin and 5.8 mg NaCl.[2,3] 1-mL and 2-mL multidose (containing preservative) vials also contain 2.5 mg human albumin, 8.2 mg NaCl, and benzyl alcohol 1% in SW.[2,3] See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.
Suitable diluents	Dilution not recommended, except in cases of SC administration with preservative-free drug.[2,3] (See Other Routes of Administration section.)
Maximum concentration	40,000 units/mL.[2]
Preparation and delivery	Avoid vigorous shaking as it can denature glycoprotein.[2] Protect solution from light.[2] For PN compatibility information, please see Appendix D.
IV push	Rapid.
Intermittent infusion	Dilute dose in 2 mL of protein-containing PN fluid or 2 mL of 5% albumin and infuse over 4 hours (to mimic the pharmacokinetics of SC dosing).[20]
Continuous infusion	Can be mixed in IV fluids containing at least 0.05% protein (amino acids).[22,32,33]

Epoetin Alfa

Other routes of administration

The SC route is preferred except in patients on hemodialysis when IV administration is preferred.[2,27] For SC administration, the dose can be diluted 1:1 with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9%. The benzyl alcohol in the bacteriostatic saline decreases the discomfort from SC injection. This is not necessary when using the multidose product that contains benzyl alcohol.[2] (See Additives section.) IM administration is not indicated.

The manufacturer recommends administering without dilution; however, it can also be diluted with an equal volume of NS and infused over 1–3 minutes. May be infused into dextrose solution when diluted with albumin.[2]

Comments

Significant adverse effects: Hypertension[2,5,7,10] and blood vessel[6] or vascular access occlusion[4,7] have occurred in children with renal failure. A 12-year-old boy with end-stage renal disease developed hypertension with encephalopathy, which resolved with discontinuation of phenytoin and erythropoietin.[34]

Transient neutropenia was associated with larger erythropoietin doses in preterm neonates.[35]

Rare adverse effects: Pure red cell aplasia, in association with neutralizing antibodies to erythropoietin (anti-EPO antibodies), has been reported as a rare yet important reaction in *adults* and children, particularly those with chronic renal failure.[2,36] Any child with a loss of response to erythropoietin should be evaluated.

Other: Failure to respond may be a result of iron deficiency.[2,16,17,27] Following the erythropoietin infusion, IV ferrous gluconate,[7] or iron dextran[20,37] may be given to patients who have inadequate iron stores and who are unable to tolerate oral iron.

Inform patients of risks associated with ESA therapy. Medication guides, available from the manufacturer, should be given to all patients receiving ESA therapy at home.[2]

Ertapenem

Brand names	Invanz
Medication error potential	ISMP lists confusion for Invanz with Avinza.[1] USP reports confusion with imipenem-cilastatin and meropenem.[2]
Contraindications and warnings	**Contraindications:** In patients with a known hypersensitivity to any component of this product or to other carbapenems or in patients who have demonstrated anaphylactic reactions to beta-lactams.[3] **Warnings** **Allergic reactions:** Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[3] These are more likely in patients who are sensitive to multiple allergens and in those with a history of penicillin, cephalosporins, or other beta-lactam hypersensitivity.[3–5] **Seizures:** Neurotoxicity of the carbapenem antibiotics has been reported.[3] Seizures occur most commonly in patients with renal impairment and/or underlying neurologic disorders. (See Comments section.) **Superinfection:** Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[3] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[3] Antibiotic use that is not directed against *C. difficile* may be discontinued.[3]
Infusion-related cautions	If a decision is made to give ertapenem to a patient with known penicillin, cephalosporins, or other beta-lactam hypersensitivity, the patient should be closely observed for allergenicity.[3] Serious anaphylactic reactions require immediate emergency treatment with epinephrine, oxygen, IV steroids, and airway management, including intubation. Other therapy may also be administered as indicated.
Dosage	Not for use in meningitis due to decreased CNS penetration.[3] **3 months to 12 years:** 30 mg/kg/day divided q 12 hr up to 1 g/day.[3,6–9] **13–17 years of age:** 20 mg/kg q 24 hr[6–9] up to 1 g/day.[3,6–9] Duration of therapy varies depending on the type and severity of infection, as well as causative organism.
Dosage adjustment in organ dysfunction	If CrCl is ≤30 mL/min, a dose decrease of 50% is recommended in *adults*.[3]
Maximum dosage	1 g/day.[3]
Additives	Contains approximately 137 mg (6 mEq) of sodium/g of ertapenem.[3,10]
Suitable diluents	NS.[3,10]
Maximum concentration	20 mg/mL.[3,10]

Ertapenem

Preparation and delivery	**Stability:** Immediately dilute reconstituted solution in NS.[3] Reconstituted solution can be stored at room temperature (25°C) and used within 6 hours or may be stored for 24 hours under refrigeration (5°C).[3] Should be used within 4 hours after removal from refrigeration.[3] **Compatibility:** Do not dilute in dextrose containing solutions.[3]
IV push	Not administered by this method.
Intermittent infusion	Over 30 minutes.[3,10]
Continuous infusion	Not administered by this method.
Other routes of administration	May be administered IM following reconstitution with 1% lidocaine HCl injection, USP (in saline without epinephrine).[3,10,11] Maximum duration of IM therapy is 7 days.[3]
Comments	**Rare adverse effects:** Neurotoxicity of the carbapenem antibiotics has been reported.[12,13] In *adults*, seizure activity related to carbapenem use most often occurs after 7 days and appears to be related to an underlying CNS disorder, impaired renal function, and/or large doses.[3,13] Because of the risk of seizures, the drug should be used cautiously in patients with CNS infections or renal dysfunction, patients with history of seizure disorders, and when used in combination with drugs that lower the seizure threshold.[3,14] If seizures occur, the need for ertapenem should be considered and the dosage should be assessed.[3] **Drug interactions:** Oral probenecid may increase serum concentrations of ertapenem.[3,8] Carbapenems may reduce serum concentrations of valproic acid, which can result in a loss of seizure control.[15] Serum valproic acid concentrations should be monitored frequently after beginning or increasing the dose of a carbapenem. Alternative antibiotics or anticonvulsant therapy should be considered if serum valproic acid concentrations drop below the therapeutic range or a seizure occurs.[3]

Erythromycin Gluceptate/Lactobionate

Brand names	Erythrocin Lactobionate-IV, Ilotycin Gluceptate
Medication error potential	Look-alike, sound-alike drug names. USP reports confusion with azithromycin.[1]
Contraindications and warnings	**Contraindications:** In patients with known hypersensitivity to erythromycin.[2] It should not be given to patients taking terfenadine or astemizole.[2] **Warnings:** Hepatic dysfunction, with or without jaundice, has been reported.[2] Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	Thrombophlebitis frequently occurs.[3]
Dosage	**Neonates:** Little information available. Seventeen neonates ≤15 days of age with birth weights ≤1500 g were given 40 mg/kg/day divided q 8 hr.[4] Fourteen infants (30.6 ± 5.4 weeks gestational age [WGA] and birth weight 1466 ± 825 g) were given 3–6 mg/kg/day divided q 8 hr for feeding intolerance.[5] Fourteen neonates ≤1500 g and ≤15 days of age received 25 or 40 mg/kg/day divided q 6 hr for a total of 10 days.[6] Evidence from studies with a small sample size have not demonstrated a reduction in chronic lung disease or death when erythromycin (prophylaxis or treatment) was given to intubated preterm infants with suspected or confirmed *Ureaplasma urealyticum*.[4,7] **Infants and children** **Mild-to-moderate infections:** Not appropriate.[8] **Severe infections:** 15–50 mg/kg/day (up to 4 g/day) divided q 6 hr or given over at least 60 minutes or by continuous infusion.[2,8] **Pelvic inflammatory disease (PID):** Although the manufacturer recommends 500 mg q 6 hr for at least 3 days followed by 7 days of oral therapy,[2] the CDC guidelines do not include erythromycin as first-line therapy for PID due to *N. gonorrhoeae*.[9] **Prokinetic agent:** Doses of 10–48 mg/kg/day divided q 6–8 hr,[10–12] continuous infusion of 3 mg/kg/hr,[12] and 1 mg/kg infused over 30 minutes followed by octreotide[13] have been used in children. At this time, there is insufficient evidence to recommend small or large dose erythromycin for preterm infants at risk of feeding intolerance.[10,14]
Dosage adjustment in organ dysfunction	If CrCl is <10 mL/min, administer 10–17 mg/kg q 8 hr.[15] Use cautiously in hepatic dysfunction.[2,16]
Maximum dosage	50 mg/kg/day[8] not to exceed 4 g/day.[2]
Suitable diluents	LR, NS,[2] D5W, NS.[17]
Maximum concentration	5 mg/mL.[2,17]

Erythromycin Gluceptate/Lactobionate

Preparation and delivery	**Stability:** Should be completely administered within 8 hours.[2] **Compatibility:** See Appendix D for PN compatibility information.[18]
IV push	Not recommended due to local irritation.[2,17]
Intermittent infusion	1–5 mg/mL over 20–60 minutes.[2,17]
Continuous infusion	Continuous infusion of 1 mg/mL is preferred to intermittent delivery.[2,17]
Other routes of administration	None.
Comments	**Rare adverse effects:** Although high-frequency sensorineural deafness occurred in a 17-year-old with renal failure,[19] this complication usually occurs in older patients.[19–21] Macrolide antibiotics may prolong cardiac repolarization and QT interval to cause cardiac arrhythmia and torsades de pointes.[2,22] Ventricular arrhythmias (in individuals with pre-existing myocardial disease), nausea, vomiting, and abdominal cramps have occurred.[2,23] Bradycardia and hypotension have been reported in neonates[24,25] and in a child.[26] Prolonging the infusion to ≥60 minutes has been recommended to decrease potential direct cardiotoxicity.[24,25] Exacerbation of symptoms of myasthenia gravis has been reported.[2] **Drug interactions:** Erythromycin is a CYP450 inhibitor.[2] Because erythromycin is associated with numerous drug interactions that may result in loss of efficacy or significant toxicity, consult appropriate resources for dosing recommendations before combining any drug with erythromycin. **Laboratory interference:** Erythromycin interferes with the fluorometric determination of urinary catecholamines.[2] **Osmolality:** 5 mg/mL in D5W and NS is 265 and 291 mOsm/kg, respectively.[17]

Esmolol HCl

Brand names	Brevibloc
Medication error potential	High-alert medication (adrenergic antagonist and antiarrhythmic) that has an increased risk of causing significant patient harm if used in error.[1] Look-alike, sound-alike drug names. Confusion between Brevibloc and Brevital has been reported.[2]
Contraindications and warnings	**Contraindications:** Hypersensitivity to esmolol HCl or any component of the formulation.[3] Should not be used in those with sinus bradycardia, heart block greater than first degree (unless functional pacemaker), cardiogenic shock, or overt heart failure.[3] **Warnings:** Use cautiously in patients with diabetes mellitus as esmolol may block hypoglycemia-induced tachycardia and blood pressure changes.[3] Use lowest dose possible in patients with a history of bronchospasm (e.g., asthma) and discontinue infusion if bronchospasm occurs.[3] Should not be used to treat hypertension due to the vasoconstriction associated with hypothermia.[3]
Infusion-related cautions	Extravasation may result in serious local reactions, including tissue necrosis.[3]
Dosage	**Antiarrhythmias (supraventricular tachycardia):** Initiate dose of 500–600 mcg/kg over 1–2 minutes.[3,4] If response is inadequate, a second loading dose of 500 mcg/kg has been given.[5] The loading dose should be followed by 200 mcg/kg/min.[4,5] If no response in 4 minutes, increase infusion by 25 mcg/kg/min[5] or 50–100 mcg/kg/min[4] q 4 min until >10% decrease in heart rate or blood pressure occurs.[4] The mean dose for control in one study was 550 mcg/kg/min, but it ranged from 400–1000 mcg/kg/min.[4,6] Maintenance doses >200 mcg/kg/min have not been shown to significantly increase benefits and are not recommended.[3] An 8-day-old with severe tachycardia secondary to neonatal tetanus received a loading dose of 1000 mcg/kg over 1 minute followed by a continuous infusion of 120 mcg/kg/min.[7] **Hypertensive crisis** **Loading dose:** 500–600 mcg/kg over 1 minute.[6,8,9] **Maintenance dose:** 100–500 mcg/kg/min initially.[8–11] Increase rate by 50–500 mcg/kg/min[7,10,11] q 5–10 min until heart rate or mean blood pressure decreases by at least 10%. **Postoperative tachycardia/hypertension** **Loading dose:** 125, 200, and 500 mcg/kg over 10–20 seconds.[12] Doses of 200[13] and 750[13] mcg/kg were used in an 18-month-old and a 15-year-old, respectively. **Maintenance dose:** Initial dose of 200 mg/kg/min should immediately follow loading dose. Infusion can be increased by 25–50 mcg/kg/min q 20 min as needed.[12,14] One study reported that postoperative cardiac patients required a mean dose of 700 mcg/kg/min to normalize blood pressure and that patients having coarctation repair required larger doses.[15] While some studies have noted that larger doses might be necessary when esmolol was used as a single antihypertensive in postoperative tachycardia/hypertension after coarctation repair,[12,13] others did not report a difference between 3 doses (125, 250, and 500 mcg/kg/min).[12]
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal dysfunction[16]; however, the half-life of the active metabolite may be increased 10-fold.[3]

Esmolol HCl

Maximum dosage	1000 mcg/kg as a single dose over 1 minute in a neonate.[7] Although the safety of doses above 300 mcg/kg/min has not been studied,[3] a 6-year-old received 1000 mcg/kg/min.[4] Hypotension commonly occurs, especially when doses exceed 200 mcg/kg/min.
Additives	Intended for single patient use as the parenteral product does not contain preservatives.[3]
Suitable diluents	D5W, LR, NS, ½NS, D5LR, D5NS, D5½NS, D5R, or D5W with KCl 40 mEq/L.[17]
Maximum concentration	20 mg/mL (commercially available).[3,17]
Preparation and delivery	**Stability:** Clear, colorless to light yellow solution.[3,17] A 10-mg/mL solution in suitable diluent is stable for at least 24 hours when refrigerated or at room temperature. Do not freeze.[3,17]
IV push	10 mg/mL given over 1–2 minutes.[3]
Intermittent infusion	Not administered by this route.
Continuous infusion	10–20 mg/mL.[3,17]
Other routes of administration	None reported.
Comments	**Rare adverse effects:** Caution should be used when abruptly discontinuing esmolol as acute tachycardia, hypertension, and/or ischemia may occur.[3] **Monitor:** Heart and respiratory rate, blood pressure, and ECG should be continuously assessed during therapy.[3] Titrate doses to achieve beta blockade (usually defined as a 10% decrease in heart rate or mean blood pressure).[3,12] If hypotension occurs, decrease the infusion rate or discontinue esmolol. Once esmolol is discontinued, effects last approximately 2–16 minutes.[4,5] **Drug interactions:** Concomitant use of morphine may increase esmolol serum concentration up to 50%.[18] A variety of drug interactions have been reported. Consult appropriate resources for dosing recommendations before combining any drug with esmolol. **Laboratory test interference:** Increases cholesterol (S) and glucose.[14] **Other:** Once a stable heart rate is achieved, transition to alternative anti-arrhythmic agents (e.g., propranolol, digoxin, or verapamil). Thirty minutes following the first dose of the alternative agent, reduce the infusion rate of esmolol by 50%. Following the second dose of the alternative agent, monitor the patient's response and if satisfactory control is maintained for the first hour, discontinue esmolol.[3]

Esomeprazole

Brand names	Nexium
Medication error potential	Look-alike, sound-alike drug names. USP reports that esomeprazole has been confused with lansoprazole; no patient harm resulted. USP also reports that Nexium has been confused with Nexavar (a high-alert chemotherapy agent), Fexium and Norvasc; no patient harm resulted.[1]
Contraindications and warnings	Esomeprazole is contraindicated in patients with a hypersensitivity to esomeprazole, substituted benzimidazoles, or any of the constituents in the formulation.[2] Proton-pump inhibitor (PPI) use has been associated with an increased risk for *Clostridium difficile*-associated diarrhea. Patients receiving PPI therapy who develop diarrhea that does not improve should be evaluated and a diagnosis of *C. diff* should be considered.[3] Studies suggest that PPI therapy increases the risk of osteoporosis-related fractures of the wrist, hip, or spine, especially in patients receiving high-doses or therapy over a year or longer.[2] It is recommended to use the lowest dose and the shortest duration of therapy appropriate for the patient's condition. Hypomagnesemia has been reported in patients receiving PPIs for at least 3 months of therapy. Patients who are expected to be on longer-term treatment, or those receiving concomitant medications that may cause hypomagnesemia should be monitored closely.[2] Use of PPIs with high-dose methotrexate may elevate and prolong serum concentrations of methotrexate and/or its metabolite leading to toxicities. Temporary withdrawal of the PPI should be considered.[2,4]
Infusion-related cautions	None.
Dosage	In *adults*, oral and IV dosage have been found to be similar in gastric acid suppression.[2] Therapy should be changed to oral route as soon as appropriate. **Infants 1 month to <1 year:** Gastroesophageal reflux: 0.5 mg/kg/day.[2] **Children 1–17 years:** The safety and efficacy of doses >1 mg/kg/day and/or treatment duration >8 weeks have not been determined.[5-8] **Gastroesophageal reflux with erosive esophagitis**[2] **<55 kg:** 10 mg every day. **≥55kg:** 20 mg every day. ***Adults*, gastroesophageal reflux with erosive esophagitis:** 20–40 mg every day for 4–8 weeks; treatment may be continued for additional 4–8 weeks if incomplete healing.[2]
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal dysfunction or in mild-to-moderate hepatic impairment. Do not exceed 20 mg/day in patients with severe hepatic disease (Child Pugh Class C).[2]
Maximum dosage	The manufacturer states 40 mg/day in *adults*; single doses of 80 mg have not been associated with adverse effects.[2]
Additives	Edetate disodium.[2]

Esomeprazole

Suitable diluents	D5W, LR, NS.[2,9]
Maximum concentration	8 mg/mL.[2]
Preparation and delivery	**Delivery:** No other medications should be given through the same IV site or tubing as esomeprazole. The IV line should be flushed with D5W, NS, or LR, before and after esomeprazole administration.[2] **Stability:** The manufacturer states that esomeprazole sodium is stable in either NS or LR for 12 hours and is stable in D5W for 6 hours.[2] Another study has found solutions of esomeprazole 0.4 and 0.8 mg/mL to be physically and chemically stable in D5W, LR, and NS for a minimum of 2 days at room temperature and 5 days refrigerated. Samples stored at room temperature and refrigerated samples reconstituted with D5W developed a yellow tint within 24 hours; this discoloration was associated with $<$10% loss of activity.[9]
IV push	4–8 mg/mL over at least 3 minutes.[2]
Intermittent infusion	Dilute reconstituted drug (4 mg/mL or 8 mg/mL) to a total volume of 50 mL with suitable diluent and infuse over 10–30 minutes.[2]
Continuous infusion	Not indicated.
Other routes of administration	No information available to support administration by other routes.
Comments	**Significant adverse effects:** Respiratory distress with chest retraction, wheezing, and facial edema occurred in an infant receiving esomeprazole; symptoms resolved with discontinuation of the esomeprazole.[10] Common adverse effects include abdominal pain, constipation, flatulence, dyspepsia, and headache.[2] Administration of PPIs has been associated with increased risk of developing gastroenteritis and pneumonia in children.[11] Prolonged use ($>$3 years) may lead to impaired absorption of cyanocobalamin (vitamin B_{12}) due to achlorhydria.[12] **Drug interactions:** Metabolized to inactive metabolites mainly by CYP2C19 and to lesser extent by CYP3A4. Esomeprazole should not be given concomitantly with Reyataz (atazanavir and nelfinavir) because it substantially lowers atazanavir plasma concentrations and decreases efficacy.[2] A known interaction exists between esomeprazole and clopidogrel. Since clopidogrel is metabolized to its active metabolite primarily via CYP2C19, and to a lesser extent, via CYP3A4 and CYP2C9, its use with esomeprazole may decrease the formation of the active metabolite and decrease antiplatelet effects.[13]

Etanercept

Brand names	Enbrel
Medication error potential	Look-alike, sound-alike drug names. ISMP reports Enbrel was confused with Levbid.[1]
Contraindications and warnings	**U.S. boxed warning** **Risk of serious infections:** Patients receiving etanercept are at risk for developing serious infections. Those with active infections should not begin treatment. Those who develop infection while on treatment should be monitored closely.[2] Patients should be evaluated for latent tuberculosis (TB) infection with a tuberculin skin test. If the skin test is positive, TB treatment should be started prior to beginning treatment with etanercept.[2] (See Comments section.) **FDA alert:** On August 4, 2009, the FDA announced that it is requiring those who manufacture tumor necrosis factor (TNF) blockers to update the box warning to include an increased risk of lymphoma and other cancers in children and adolescents treated with TNF blockers.[3] **Contraindications:** Patients who have sepsis should not be given etanercept.[2] Those who have had a previous severe hypersensitivity reaction to etanercept should not receive any additional doses.[2] **Other warnings:** Anaphylactic type reactions have been reported.[3] Appropriate medical care should be available in the event this occurs. The needle cover of the prefilled syringes and autoinjector contains latex. Those with latex allergy should not handle the syringes.[2,4]
Infusion-related cautions	Not intended for IV use.
Dosage	**Polyarticular-course juvenile idiopathic arthritis (JIA) in children ≥2 years**[2,4–6]**:** 0.4 mg/kg up to 25 mg twice weekly or 0.8 mg/kg up to 50 mg once a week. <31 kg should be dosed from the multidose vial and not a prefilled syringe. ≥63 kg may use the 50-mg prefilled syringe. **Psoriasis**[7–9]**:** 0.4 mg/kg twice weekly or 0.8 mg/kg (up to 50 mg) once a week. **Chronic uveitis**[10–12]**:** 0.4 mg/kg up to 25 mg twice weekly. Infliximab may be more effective in preventing uveitis than etanercept.[12,13] (See Comments section.)
Dosage adjustment in organ dysfunction	No data available.
Maximum dosage	50 mg once a week.
Additives	Multidose vials contain benzyl alcohol.[2,4] (See Appendix D for specific information about potential benzyl alcohol toxicity in neonates.)
Suitable diluents	Not diluted.

Etanercept

Maximum concentration	50 mg/mL.
Preparation and delivery	**Preparation:** The multidose vial is reconstituted with 1 mL BW that is included. The product literature should be consulted for detailed instructions. Available as disposable, prefilled syringes, or prefilled SureClick autoinjector (25 mg/0.5 mL, 50 mg/mL). Must be refrigerated until use.(2) **Delivery system issues:** Allow to come to room temperature (~15–20 minutes) prior to injection. Do not remove the needle cover until ready to inject. **Stability:** Etanercept reconstituted from the multidose vial must be discarded after 14 days.
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	Not indicated.
Other routes of administration	Administer by SC injection.
Comments	A negative skin test for TB does not rule out the possibility of disease since patients with immune diseases may exhibit cutaneous anergy.(14) Etanercept treatment improved longitudinal growth in prepubertal children with JIA.(15) Juvenile idiopathic arthritis, juvenile rheumatoid arthritis, and juvenile chronic arthritis may be used interchangeably. **Drug interactions:** Patients receiving anakinra and abatacept should not receive etanercept due to a possible increased risk for infection.[2] Live virus vaccines (measles-mumps-rubella, varicella, rotavirus) should be avoided during treatment.[2,4] **Adverse effects:** Injection site reactions include erythema and/or itching, pain, or swelling. These usually decrease in frequency with continued treatment.(2) Rare cases of inflammatory bowel disease have been reported in JIA patients receiving etanercept.[16–17]

Ethacrynate Sodium

Brand names	Sodium Edecrin
Medication error potential	None noted.
Contraindications and warnings	**Contraindications:** Infants, patients with anuria, and those with hypersensitivity to ethacrynate.[1] **Warnings:** Ethacrynic acid is a potent diuretic that may lead to significant water and electrolyte loss.[1]
Infusion-related cautions	Deafness (reversible or permanent), acute vertigo, and tinnitus have occurred, most commonly in patients with severe renal dysfunction, those receiving larger than recommended doses, or those concomitantly receiving other ototoxic drugs.[1] (See Comments section.)
Dosage	0.5–1 mg/kg; repeat if needed q 8–24 hr.[2–6] A small case series of patients with cor pulmonale due to cystic fibrosis reported a dosing regimen of 1 mg/kg/dose repeated as necessary q 30 min up to a maximum of 3 mg/kg.[7]
Dosage adjustment in organ dysfunction	No dosage decrease required in patients with renal dysfunction.[8] Use with caution in patients with advanced cirrhosis.[1]
Maximum dosage	1.7 mg/kg/dose,[2] not to exceed 100 mg/dose in *adults*.[1]
Additives	Contains 0.165 mEq sodium/50 mg of ethacrynic acid equivalent.[9]
Suitable diluents	D5W, NS, R, LR.[9] Reconstitution with D5W products with a pH <5 results in hazy or opalescent solutions. These should not be used.[1,9]
Maximum concentration	2 mg/mL.[2]
Preparation and delivery	Reconstitute to 1 mg/mL.[1]
IV push	Not recommended.[1]
Intermittent infusion	Slowly, over several minutes through a running IV infusion solution.[1] (See Comments section.)
Continuous infusion	Not indicated.
Other routes of administration	Should not be given IM or SC because of local pain and irritation.[1]

Ethacrynate Sodium

Comments

Ethacrynate sodium may be used to manage edema in patients with impaired renal function.[1]

Alternating doses of ethacrynic acid with furosemide may not overcome diuretic resistance.[5]

Adverse effects: Local pain and irritation at the infusion site have occurred.[1]

The duration of treatment is directly related to the development of sensorineural hearing loss in neonates with persistent pulmonary hypertension.[10] Investigators point out that this may be transient; however, they suggest that infusion over at least 5–10 minutes may be protective.[10] In a retrospective review analyzing the correlation between ototoxic drugs and the development of hearing loss in children who underwent surgical palliation for hypoplastic left heart syndrome, two of the four patients who received ethacrynic acid developed permanent hearing loss. The cumulative dose in these patients was (mean ± SD) 3.9 ± 3.3 mg/kg.[11]

In *adults*, irreversible deafness[12] and upper GI bleeding[13] have occurred following infusion.

Electrolyte abnormalities, including hypokalemia, occur.

Monitoring: Serum potassium concentration.[1]

Ethanol

Brand names

Dehydrated alcohol injection, USP

Medication error potential

Look-alike, sound-alike drug name. Ethanol may be confused with Ethyol or Ethamolin.[1]

Contraindications and warnings

Hypersensitivity to ethyl alcohol[2]; seizure disorder and diabetic coma[2]; subarachnoid injection of dehydrated alcohol in patients receiving anticoagulants due to risk of bleeding.[2,3]

Use with caution in patients who have diabetes, hepatic impairment, gout, and shock. Also, cautiously following cranial surgery or in patients with anticipated postpartum hemorrhage.[2]

Infusion-related cautions

None reported.

Dosage

Treatment of methanol or ethylene glycol ingestion

Loading dose: 8–10 mL/kg of 10% ethanol solution, not to exceed 200 mL.[2]

Maintenance dose (see table below)[2]: Continue infusion until methanol or ethylene glycol blood concentration is <10 mg/dL.[2]

	Nondrinker	Average Drinker	Chronic Drinker
EtOH dosage (by weight)	66 mg/kg/hr	110 mg/kg/hr	154 mg/kg/hr
IV: 10% EtOH (7.9 g EtOH/dL)	0.83 mL/kg/hr	1.4 mL/kg/hr	2 mL/kg/hr

Ethanol lock therapy

Treatment of fat occlusion of central venous catheter (CVC): Instill 70% ethanol solution at a volume equal to the internal volume of the catheter (up to 3 mL or maximum of 0.55 mL/kg). May repeat if patency is not restored after an initial 30-minute dwell time. If the dose is repeated, reassess after 4-hour dwell time.[2]

Prevention or treatment of central line associated bloodstream infection: Instill a volume equal to the internal volume of the catheter and allow solution to dwell in the CVC for allotted time period. Dwell times range from 0.25 hours to greater than 48 hours.[4–15] The reported volume of commonly used silicone catheters ranges from 0.15–1.8 mL.[16] Ethanol concentrations of 25% to 70% have been used for prevention or treatment of central line associated bloodstream infection in children.[4,6–15,17]

Dosage adjustment in organ dysfunction

Maintenance dose for treatment of methanol or ethylene glycol ingestion should be adjusted for hemodialysis. Since ethanol clearance is variable between patients, adjust the dose based on serum ethanol concentrations.[2]

Maximum dosage

Treatment of methanol or ethylene glycol ingestion: Loading dose should not exceed 200 mL.[2]

For ethanol lock therapy, a maximum of 3 mL or 0.55 mL/kg of 70% solution is recommended.[2]

Additives

None reported.

Suitable diluents

D5W or D10W for treatment of ingestion[2] and SW for ethanol lock therapy.[2,4,7,18]

Ethanol

Maximum concentration	10% for treatment of methanol or ethylene glycol ingestion[2]; 70% for treatment of fat occlusion in CVC[2]; up to 100% has been used for prevention of CVC-associated bloodstream infection in an *adult* patient,[17] but most pediatric studies use a maximum concentration of 70%.[4,6–10,12–15]
Preparation and delivery	**Storage:** Keep in a cool place, away from any heat source as ethyl alcohol is flammable.[2,3] **Stability:** Solutions have been shown to be stable for at least 14–28 days.[19,20] **Delivery system issues:** In silicone catheters, prolonged exposure (up to 9 weeks) to 30% to 70% ethanol solutions did not affect the structural integrity of the catheter.[21–23] There have been conflicting reports for effect of prolonged ethanol exposure on polyurethane catheters. Studies reported measurable effects on polyurethane catheters after exposure to 30% to 100% ethanol concentrations.[24,25] However, one study reported no significant effects on structural integrity after exposure to 70% ethanol for up to 9 weeks.[22] **Compatibility:** Ethanol is not compatible with solutions containing heparin.[19] It is recommended to flush well with NS before and after ethanol lock therapy.[19]
IV push	Once ethanol lock therapy is completed, some pediatric studies report slowly flushing the solution through the catheter,[8,9,11,12,14,15] while others report withdrawal of the solution from the CVC.[4,6,7,10,13]
Intermittent infusion	When treating methanol or ethylene glycol ingestion, infuse the loading dose plus the first hour of the maintenance dosing over 60 minutes.[2]
Continuous infusion	Treatment of methanol or ethylene glycol ingestion (see chart in the Dosage section).[2]
Other routes of administration	Intraneural (for therapeutic neurolysis).[2,3]
Comments	**Adverse effects:** Ethanol is primarily metabolized by the liver and has been associated with hepatotoxicity.[26] Central venous catheter thrombosis[8,9,27] and occlusion[28] have been reported in patients receiving ethanol lock therapy. Deep vein thrombosis in the same leg as the CVC was also reported in one patient.[4]

Etomidate

Brand names	Amidate, generic
Medication error potential	ISMP high-alert medication (moderate sedation agent) that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports confusion with Trandate.[2] May be confused with etidronate.[3]
Contraindications and warnings	**Contraindications:** Should not be used in a person with known hypersensitivity to etomidate.[4] **Warnings:** Should only be given by persons trained in the administration of general anesthetics and management of their complications.[4] May cause suppression of endogenous cortisol and aldosterone and is *not* intended for prolonged infusion.[4] (See Significant Adverse Effects in the Comments section.)
Infusion-related cautions	Avoid administration into small vessels.[4] Transient pain at the injection site may be managed by preadministration with lidocaine (0.5 mg/kg).[5] Involuntary muscle movements have been reported (30% of patients).[4]
Dosage	Etomidate is not recommended for children <10 years of age because of lack of sufficient safety and efficacy data.[4] Current evidence suggests etomidate should be avoided in children with known or suspected septic shock.[6,7] (See Significant Adverse Effects in the Comments section.) **Sedation:** 0.3 mg/kg given over 30–60 seconds[4,8–10]; usual dosing range is between 0.2–0.6 mg/kg,[4,5,11–15] with maximum single doses reported as 10 mg[13] or 20 mg.[16] Loss of consciousness generally occurs within 60 seconds of administration.[4] The manufacturer recommends against administering etomidate for prolonged periods as a continuous infusion due to the potential for adrenal suppression[4,17] and propylene glycol toxicity.[18] In severely stressed patients, consider the need for cortisol replacement.[4] **Severe hypercortisolemia:** 0.03–0.1 mg/kg/hr.[19–23]
Dosage adjustment in organ dysfunction	No dosage adjustment is necessary in renal dysfunction.[24] No dosing adjustment is recommended for patients with cirrhosis; however, the duration of action may be prolonged.[4] In *adults* with obstructive jaundice, a lower dose was required (0.15 mg/kg versus 0.2 mg/kg) to reach an equivalent level of sedation, and the dosing requirement was negatively correlated with total bilirubin values.[25]
Maximum dosage	1.1 mg/kg as a single dose.[14]
Additives	Contains propylene glycol 35%.[4,26] (See Appendix C for specific information about propylene glycol's potential for toxicity.)
Suitable diluents	Administered undiluted.
Maximum concentration	2 mg/mL (commercially available).[4]

Etomidate

Preparation and delivery	**Stability:** Do not administer unless solution is clear.[4]
IV push	Over 30–60 seconds.[4]
Intermittent infusion	No information.
Continuous infusion	Not recommended for patients with severe stress or septic shock. Prolonged infusion increases risk of adverse effects.[4,18] (See Significant Adverse Effects in the Comments section.)
Other routes of administration	None.
Comments	**Significant adverse effects:** Etomidate inhibits 11-B-hydroxylase, an enzyme necessary for the production of cortisol, aldosterone, and corticosterone.[3] This suppression does not appear to be dose related and has been noted after a single dose.[27] An increase in adrenal insufficiency and mortality was reported among critically ill and multitrauma patients receiving etomidate infusions.[17,28] *Pediatric Advanced Life Support* guidelines recommend against routine use of etomidate in patients with septic shock.[6] Until the risk for developing adrenal insufficiency has been assessed in a large, randomized controlled trial, alternative agents (e.g., midazolam, pentobarbital, or ketamine) should be considered for sedation in this patient population. **Rare adverse effects:** Etomidate can increase EEG activation with epileptiform spikes and large doses have caused EEG slowing and isoelectricity.[3] Transient skeletal muscle movements occur in 30% to 50% of patients.[4] While the movements are usually bilateral and predominately myoclonic,[29,30] tonic, ocular, and averting movements have been reported. Movements appear to be more frequent in patients who also manifest venous pain on injection.[4] Administration of a benzodiazepine or fentanyl may decrease movements.[4] One report noted successful termination with dantrolene.[29]

Etoposide

Brand names	Toposar, VePesid, VP-16, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1]
Contraindications and warnings	**U.S. boxed warning:** Etoposide should be administered under the supervision of a qualified physician. Severe myelosuppression with resulting infection or bleeding may occur.[2] **Contraindications:** Etoposide is contraindicated in patients who have a hypersensitivity to etoposide or any of the components of the formulation.[2] **Other warnings:** May cause myelosuppression, hypotension, severe emesis (see Significant Adverse Effects in the Comments section) and anaphylaxis.[2,3]
Infusion-related cautions	Hypotension has been reported with rapid administration of etoposide.[2] Stop or slow the rate of the infusion, and administer IV fluids if necessary.[3] Infusing etoposide at a rate slower than 100 mg/m^2/hr (or 3.3 mg/kg/hr) has been shown to minimize hypotensive effects.[3] Anaphylactic reactions have been seen with etoposide administration, manifesting as bronchospasm, tachycardia, dyspnea, and hypotension. Higher rates of anaphylaxis have been seen in children that receive higher than recommended concentrations of etoposide.[2] Extravasation has occurred but has rarely been associated with necrosis.[2] (See Appendix E for additional information regarding extravasation treatment.)
Dosage	Consult individual protocol for complete dosing information. Etoposide is used as a component of combination therapy or as single agent therapy in multiple pediatric and hematologic neoplasms. A general dosage regimen has included 60–150 mg/m^2/day IV for 2–5 days q 3–6 wk.[4,5] Specific regimens include the following: **Acute myeloid leukemia** **Remission induction:** 150 mg/m^2 for 2–3 days for two to three cycles.[4–5] **Intensification/consolidation:** 250 mg/m^2/day for 3 days, for courses two through five.[3–5] **Brain tumor:** 150 mg/m^2 on days 1–3 or days 2–3 of treatment course.[3,6] **Neuroblastoma or osteosarcoma:** 100 mg/m^2 over 1 hour on days 1–5 of cycle or 75 mg/m^2 over 1 hour on days 1–4 of weeks 4–9 in combination with other chemotherapeutic agents.[3,7–9] **High-dose conditioning regimen for allogeneic bone marrow transplant (BMT):** 60 mg/kg as a single dose in combination chemotherapy.[3,10,11] **BMT conditioning for rhabdomyosarcoma or neuroblastoma:** 160 mg/m^2/day IV continuous infusion for 4 days.[3]
Dosage adjustment in organ dysfunction	The manufacturer recommends to reduce the dose by 25% in patients with a CrCl of 15–50 mL/min and that no data exists on patients with CrCl <15 mL/min but that further dosage reductions are likely to be necessary.[2] Another reference recommends a dose reduction of 25% in patients with CrCl of 10–50 mL/min and a 50% dose reduction in patients with a CrCl <10 mL/min.[12]

Dosage adjustment in organ dysfunction *(cont.)*	Use caution in patients with hepatic dysfunction.[3] Specifically, a 50% dosage reduction is recommended for patients with a serum bilirubin of 1.5–3 mg/dL and a 75% dosage reduction for a serum bilirubin >3 mg/dL.[3] Another source recommends that if the serum bilirubin is 1.5–3 mg/dL or the aspartate aminotransferase (AST) is 60–180 units/L, the dosage should be reduced by 50%; if the bilirubin is 3–5 mg/dL or AST >180, reduce the dosage by 75%; and if bilirubin is >5 mg/dL, do not administer.[13]
Maximum dosage	Not established.
Additives	Each mL contains 30 mg benzyl alcohol.[2,14] (See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.)
Suitable diluents	D5W or NS.[2]
Maximum concentration	0.2–0.4 mg/mL.[2,14] Precipitation has developed with concentrations >0.4 mg/mL.[14]
Preparation and delivery	The surfactant component may alter drop size. Administration with infusion devices that do not operate via drop size is recommended.[14] Administration devices made up of acrylic or acrylonitrile, butadiene, and styrene (ABS) should be avoided, as they have cracked and leaked when used with undiluted etoposide.[2]
IV push	Not recommended.[2,14] Rapid administration has been associated with the development of hypotension. (See Infusion-Related Cautions section.)
Intermittent infusion	0.2–0.4 mg/mL may be infused over at least 30–60 minutes.[2,14] If volume is a concern, it may be infused over a longer time period, up to 210 minutes.[2,3]
Continuous infusion	Has been administered as a continuous infusion over 5 days.[3] To minimize hypotensive reactions, rate should not exceed 100 mg/m^2/hr (or 3.3 mg/kg/hr) at final concentration of 0.2–0.4 mg/mL. High-dose etoposide administered as a continuous infusion has been associated with more nonhematological toxicities compared to intermittent infusions.[15]
Other routes of administration	IT, IP, and intrapleural administration are not recommended.
Comments	**Significant adverse effects:** Etoposide is associated with a low (10% to 30%) risk of emesis.[16] Patients should receive antiemetic therapy to prevent acute and delayed nausea and vomiting. The recommended therapy is a corticosteroid on every day chemotherapy is administered; alternatives are a phenothiazine (e.g., prochlorperazine) or a butyrophenone (e.g., droperidol).[16,17] Therapy for delayed nausea and vomiting is generally not needed. Breakthrough medications should also be offered. Selection should be based on what the patient is currently receiving for acute emesis prophylaxis. **Monitoring:** CBC with platelets, vital signs, renal function, bilirubin, and hemoglobin.[2,3] **Drug interactions:** Etoposide is a major substrate for CYP3A4, a minor substrate for CYP1A2 and 2E1, and a weak inhibitor for CYP2C9 and 3A4. The potential for drug interactions exists. Cyclosporine may substantially increase exposure to etoposide by decreasing metabolism.[3] Consult appropriate resources for dosing recommendations before combining any drug with etoposide.

Factor IX (Human)

Brand names

AlphaNine SD, BeneFIX, Mononine

Medication error potential

Factor IX may be confused with Factor IX complex.[1]

Contraindications and warnings

Contraindications: Hypersensitivity or intolerance to any component in the product.[2–4] Product-specific contraindications:

BeneFIX: Known hypersensitivity to hamster protein.[3]

Mononine: Known hypersensitivity to mouse protein.[4]

Other warnings: All products contain polysorbate 80, which may cause allergic reactions in susceptible individuals, especially neonates.[2–4]

AlphaNine SD and Mononine are prepared from human pooled plasma and may carry a risk for transmission of infectious agents, despite viral attenuation processes.[2,3,5,7] Hepatitis A and B vaccination are recommended in all hemophilia patients.[7]

Serious and potentially fatal thrombosis or disseminated intravascular coagulation may occur in patients with hepatic impairment and in patients undergoing surgery. Use with caution in patients with liver disease, neonates, postoperatively, or patients with signs of fibrinolysis. Monitor all patients closely for thromboembolic complications.[2–4,6]

Hypersensitivity and anaphylactic reactions have been reported with all Factor IX products, usually in association with the development of Factor IX inhibitors. Delayed reactions in previously untreated patients may occur. Patients should be closely monitored between the 10th and 20th exposure day.[2–4]

Nephrotic syndrome has been reported following immune tolerance induction with Factor IX products in Hemophilia B patients with Factor IX inhibitors and a history of severe allergic reactions to Factor IX.[2–4]

Infusion-related cautions

All products have been associated with reactions such as urticaria, fever, chills, nausea, vomiting, headache, somnolence, lethargy, flushing, or tingling. Reduce infusion rate or use a different lot.[2–4]

Dosage

Individualize dosage based on severity of Factor IX deficiency, extent, and location of bleeding and the patient's clinical status.[5]

Formula for International Units required to raise blood level %

AlphaNine SD: Number of Factor IX International Units required = bodyweight (kg) × desired Factor IX level increase (% normal) × 1 International Unit/kg.[2]

BeneFIX

<15 years: Number of Factor IX International Units required = bodyweight (kg) × desired Factor IX level increase (% normal) × 1.4 International Units/kg.[3]

≥15 years: Number of Factor IX International Units required = bodyweight (kg) × desired Factor IX level increase (% normal) × 1.3 International Units/kg.[3]

Mononine: Number of Factor IX International Units required = bodyweight (kg) × desired Factor IX level increase (% normal) × 1 International Units/kg.[4]

Hemorrhages

Minor hemorrhage (bruises, cuts or scrapes, uncomplicated joint hemorrhage)

AlphaNine SD: Raise Factor IX levels to 20% to 30% of normal. Typical dose: 20–30 International Units Factor IX/kg q 12 hr until hemorrhage stops and healing has been achieved (about 1–2 days).[2]

Dosage *(cont.)*

BeneFIX: Raise Factor IX level to 20% to 30% of normal. Dose q 12–24 hr for 1–2 days.[3]

Mononine: Raise Factor IX level to 15% to 25% of normal. Initial loading dose up to 20–30 International Units/kg administered once and repeated in 24 hours if needed.[4]

Moderate hemorrhage (nose bleeds, mouth and gum bleeds, dental extractions, hematuria)

AlphaNine SD: Raise Factor IX levels to 25% to 50% of normal. Typical dose: 25–50 International Units Factor IX/kg q 12 hr until healing has been achieved, usually 2–7 days.[2]

BeneFIX: Raise Factor IX level to 25% to 50% of normal. Dose q 12–24 hr until bleeding stops and healing begins, usually 2–7 days.[3]

Mononine: Raise Factor IX level to 20% to 30% of normal. If repeat doses needed, administer q 24 hr.[4]

Major hemorrhage (joint and muscle hemorrhages, major trauma, hematuria, intracranial and intraperitoneal bleeding)

AlphaNine SD: Raise Factor IX level to 50% for at least 3–5 days. Typical dose: 30–50 International Units Factor IX/kg q 12 hr. Following this period, FIX levels should be maintained at 20% (20 International Units Factor IX/kg q 12 hr) until healing has been achieved. May require up to 10 days of treatment.[2]

BeneFIX: Raise Factor IX level to 50% to 100% of normal. Dose q 12–24 hr for 7–10 days or until adequate wound healing occurs.[3]

Mononine: Raise Factor IX level to 25% to 50% of normal. Initial loading dose up to 75 International Units/kg administered q 18–30 hr, depending on half-life and measured Factor IX levels. Continue treatment up to 10 days, depending on nature of insult.[4]

Surgical procedures

AlphaNine SD: Raise Factor IX level to 50% to 100% of normal preoperatively. Typical dose: 50–100 International Units Factor IX/kg q 12 hr. Postoperatively, maintain levels at 50% to 100% of normal for 7–10 days, or until healing has been achieved.[2]

BeneFIX: Raise Factor IX level to 50% to 100% of normal preoperatively. Dose q 12–24 hr for 7–10 days or until healing has been achieved.[3]

Mononine: Raise Factor IX level to 50% to 100% of normal immediately prior to the procedure. Repeat dose q 18–30 hr depending on half-life and measured Factor IX levels for up to 10 days.[4]

Prophylaxis, primary: 25–40 International Units/kg twice weekly or 15–30 International Units/kg 2–3 times weekly.[7,8] Individualize regimen based on age, venous access, and activity.

Dosage adjustment in organ dysfunction

No dosage adjustment required.[2–4]

Maximum dosage

Mononine: 75 International Units/kg.[4]

Additives

AlphaNine SD contains ≤0.04 International Units heparin, 0.2 mg dextrose, and ≤1 mcg polysorbate 80. Also contains trace amounts of Factors II, VII, and X.[2]

BeneFIX contains histidine (8 mM), 0.234% NaCl, 0.8% sucrose, glycine (208 mM), and polysorbate 80.[3]

Mononine contains histidine (10 mM), NaCl, mannitol (3%), and polysorbate 80 (0.0075%). Also contains trace amounts of Factors II, VII, and X.[4]

Factor IX (Human)

Suitable diluents	**Reconstitution:** Sterile water for injection (AlphaNine SD and Mononine).[2,4] 0.234% NaCl (BeneFIX).[3] Use provided diluents.
Maximum concentration	None.
Preparation and delivery	Allow product to come to room temperature before reconstitution. Use transfer needle provided or syringe and needle to transfer diluent into vial of drug. Gently swirl or rotate vial after addition of diluent. Do not vigorously shake vial. Do not refrigerate after reconstitution; administer within 3 hours after reconstitution.[2–4]
IV push	Not recommended.
Intermittent infusion	Infuse slowly; individualize rate of administration for patient comfort. **Maximum rate of infusion** **AlphaNine:** 10 mL/min.[2] **BeneFIX:** Administer over several minutes.[3] **Mononine:** 2 mL/min.[4]
Continuous infusion	Not recommended.
Other routes of administration	Not recommended.
Comments	The relative content of Factor IX in these products varies from lot to lot and product to product. Products are indicated for use in hemophilia B (Factor IX deficient) patients only.

Factor IX Complex (Human)

Brand names

Bebulin VH, Profilnine SD

Medication error potential

Factor IX complex may be confused with Factor IX.[1]

Contraindications and warnings

Contraindications: Hypersensitivity or intolerance to any component in the product.[2–3] Product-specific contraindications.

Other warnings: Bebulin VH contains dry natural rubber latex.[2] Profilnine SD contains polysorbate 80, which may cause allergic reactions in susceptible individuals, especially neonates.[3]

Factor IX complex is prepared from human pooled plasma and may carry a risk for transmission of infectious agents, despite heat treatment or other viral attenuation processes.[2–3] Hepatitis A and B vaccination are recommended in all hemophilia patients.[4]

Serious and potentially fatal thrombosis or disseminated intravascular coagulation may occur in patients with hepatic impairment and in patients undergoing surgery. Monitor all patients closely for thromboembolic complications.[2–3,5]

Infusion-related cautions

All products have been associated with reactions such as urticaria, fever, chills, nausea, vomiting, headache, somnolence, lethargy, flushing, or tingling. Reduce infusion rate or use a different lot.[2–3,5]

Dosage

Individualize dosage based on severity of Factor IX deficiency, extent and location of bleeding, and the patient's clinical status.[6]

Formula for International Units required to raise blood level %

Bebulin VH: 1 International Unit/kg of Factor IX will increase plasma Factor IX level by 0.8%.[2]

Number of Factor IX International Units required = bodyweight (kg) × desired Factor IX increased (as % of normal) × 1.2.

Profilnine SD: 1 International Unit/kg of Factor IX will increase plasma Factor IX level by 1%.[3]

Number of Factor IX International Unit required = bodyweight (kg) × desired Factor IX increase (as % of normal) × 1 International Unit/kg.

Hemorrhages

Minor hemorrhage (early hemarthrosis, minor epistaxis, gingival bleeding, mild hematuria)

Bebulin VH: Raise Factor IX level to 20% of normal. Typical initial dose: 25–35 International Units/kg once.[2]

Profilnine SD: Raise Factor IX level to 20% to 30% of normal. Single dose is usually needed.[3]

Moderate hemorrhage (severe joint bleeding, early hematoma, major open bleeding, minor trauma, minor hemoptysis, hematemesis, melena, major hematuria)

Bebulin VH: Raise Factor IX level to 40% of normal. Typical initial dose: 40–55 International Units/kg q 24 hr for 2–3 doses or until adequate wound healing. Do not raise ≥60% in patients who may be predisposed to thrombosis.[2]

Profilnine SD: Raise Factor IX level to 20% to 30% of normal. If repeat doses needed, administer q 24 hr.[3]

Dosage *(cont.)*

Severe/life-threatening hemorrhage (severe hematoma, major trauma, severe hemoptysis, hematemesis, and melena)

Bebulin VH: Raise Factor IX level to ≥60% of normal. Typical initial dose: 60–70 International Units/kg q 24 hr for 2 doses or until adequate wound healing.[2]

Profilnine SD: Raise Factor IX level to 30% to 50% of normal. Repeat dose q 24 hr until adequate wound healing.[3]

Surgical procedures

Dental surgery

Bebulin VH: Raise Factor IX level to 40% to 60% of normal on day of surgery. Typical dose: 50–60 International Units/kg administered 1 hour prior to surgery. For extraction of multiple teeth, replacement therapy may be required for up to 1 week using the same doses as for minor surgery.[2]

Profilnine SD: Raise Factor IX level to 50% of normal immediately prior to the procedure. Repeat dose q 24 hr if bleeding occurs.[3]

Minor surgery

Bebulin VH: Raise Factor IX level to 40% to 60% of normal on day of surgery. Typical initial dose: 50–60 International Units/kg administered 1 hour prior to surgery. During initial postoperative period (1–2 weeks or until adequate wound healing), decrease Factor IX level from 40% of normal to 20% of normal. Typical dose: 55 International Units/kg decreasing to 25 International Units/kg. Average dosing period may be q 12 hr initially, then q 24 hr.[2]

Profilnine SD: Raise Factor IX level to 30% to 50% of normal for at least 1 week following surgery.[3]

Major surgery

Bebulin VH: Raise Factor IX level to ≥60% of normal on day of surgery. Typical initial dose: 70–95 International Units/kg administered 1 hour prior to surgery. Do not raise >60% in patients predisposed to thrombosis. During initial postoperative period (1–2 weeks), decrease Factor IX level from 60% of normal to 20% of normal. Typical dose: 70 International Units/kg decreasing to 35 International Units/kg. In late postoperative period (≥3 weeks), further decrease to maintain Factor IX level of 20% of normal and continue until adequate wound healing. Typical dose: 35 International Units/kg decreasing to 25 International Units/kg. Average dosing period may be q 12 hr initially, then q 24 hr.[2]

Profilnine SD: Raise Factor IX level to 30% to 50% of normal for at least 1 week following surgery.[3]

Prophylaxis (may be given on a regular schedule to prevent bleeding)

Bebulin VH: 20–30 International Units/kg once or twice weekly may reduce the frequency of spontaneous hemorrhage. Individualize regimen.[2]

Dosage adjustment in organ dysfunction

No dosage adjustment required.[2–3]

Maximum dosage

None reported.

Additives

Bebulin VH contains ≤0.15 International Units heparin/International Units Factor IX.[2]

Profilnine SD contains ≤2.5 mcg polysorbate 80, when reconstituted with SW.[3]

Factor IX Complex (Human)

Suitable diluents	**Reconstitution:** SW.[2–3]
Maximum concentration	None.
Preparation and delivery	Allow product to come to room temperature before reconstitution. Use transfer needle provided or syringe and needle to transfer diluent into vial of drug. Gently swirl or rotate vial after addition of diluent. Do not vigorously shake vial. Do not refrigerate after reconstitution; administer within 3 hours after reconstitution.[2–3]
IV push	Not recommended. Rapid infusion may cause vasomotor symptoms.[5]
Intermittent infusion	Infuse slowly; individualize rate of administration for patient comfort. **Maximum rate of infusion** **Bebulin VH:** 2 mL/min.[2] **Profilnine SD:** 10 mL/min.[3]
Continuous infusion	Not recommended.
Other routes of administration	Not recommended.
Comments	The relative content of Factor IX in these products varies from lot to lot and product to product. Products are indicated for use in hemophilia B (Factor IX deficient) patients only. Factor IX complex products are concentrates of Factor IX, Factor II, and Factor X with low amounts of Factor VII.[2–3,6]

Famotidine

Brand names	Generic
Medication error potential	Look-alike, sound-alike drug names. USP reports that famotidine has been confused with fluoxetine, furosemide, lisinopril, and paroxetine.[1]
Contraindications and warnings	Known hypersensitivity to the drug or its additives. Cross-sensitivity with other H2-blockers may occur.[2]
Infusion-related cautions	None known.
Dosage	**Neonates:** 0.5 mg/kg q 24 hr.[2,3] **Infants and children:** 0.5–2.4 mg/kg/day divided q 8–12 hr.[2,4–11]
Dosage adjustment in organ dysfunction	Adjust dosage in patients with severe renal dysfunction.[2,12,13] **CrCl 30–50 mL/min:** 0.5 mg/kg/day q 24 hr.[13] **CrCl 10–29 mL/min:** 0.25 mg/kg/day q 24 hr.[13] **CrCl <10 mL/min:** 0.125 mg/kg/day q 24 hr.[13] Supplement doses above for hemodialysis and peritoneal dialysis (0.125 mg/kg/day q 24 hr) and continuous renal replacement therapy (0.5 mg/kg/day q 24 hr).[13] Another source recommends the following dose adjustment: CrCl >50 mL/min, 0.5 mg/kg (maximum 20 mg) q 12–24 hr[12]; CrCl 10–50 mL/min, increase interval to q 36–48 hr[12]; CrCl <10 mL/min, increase interval to q 72–96 hr or give 0.25 mg/kg (maximum 10 mg) q 36–48 hr.[12]
Maximum dosage	Usually 40 mg/day.[2] In one study, children who failed to respond to lower doses were given 2 doses of 1.6 mg/kg (≤40 mg) 8 hours apart.[6]
Additives	Each 50 mL of the premixed injection contains 450 mg sodium chloride (7.8 mEq sodium).[14] Multidose vials contain benzyl alcohol 0.9% as a preservative.[2,14] See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.
Suitable diluents	NS, D5W, D10W, LR, or SW.[2,14] May be diluted (0.2 mg/mL) with sodium bicarbonate 5%; concentrations >0.2 mg/mL may form precipitates.[2]
Maximum concentration	4 mg/mL.[2,14]
Preparation and delivery	Stable in PN[14,15] and TNA[14,16] solutions for 24 hours at room temperature. (See Appendix D for additional PN compatibility information.)

Famotidine

IV push	Infuse (2 mg/mL) over ≥2 minutes[2] and ≤10 mg/min.[14]
Intermittent infusion	Infuse (0.2 mg/mL) over 15–30 minutes.[2,14]
Continuous infusion	In *adults*, the total daily dose has been added to a compatible fluid and infused over 24 hours.[17]
Other routes of administration	No information available to support administration by other routes.
Comments	**Significant adverse effects:** Cardiovascular adverse effects (negative inotropic effect) have occurred in *adults* on famotidine.[18] **Pharmacokinetic considerations:** Clearance is decreased and half-life increased in infants up to 3 months of age compared to infants >3 months, children, and *adults*.[2] **Pharmacodynamic considerations:** Duration of acid suppression is longer in infants up to 3 months of age compared to older infants, children, and *adults*.[2] Two of 18 critically ill children failed to respond to 2 doses of 1.6 mg/kg (≤40 mg) given 8 hours apart.[6] Prolonged dosing has been associated with decreased duration of effect.[6] **Other:** H2-blocker therapy has been associated with the incidence of necrotizing enterocolitis in very low birth weight infants.[19,20]

Fenoldopam

Brand names	Corlopam, generic
Medication error potential	None known.
Contraindications and warnings	None known.[1]
Infusion-related cautions	Rapid titration of dose may cause hypotension.[1] Reflex tachycardia occurs with larger doses.[1–3] Tachycardia in pediatric patients receiving doses >0.8 mcg/kg/min lasted for at least 4 hours.[1]
Dosage	**Controlled hypotension during surgery (children)[1–3]:** 0.3–0.5 mcg/kg/min increased by 0.3–0.5 mcg/kg/min q 20–30 min. In one study, 0.8 mcg/kg/min (range 0.05–3.2 mcg/kg/min) was the most effective dose; no effect on blood pressure <0.2 mcg/kg/min while larger doses (>1–1.2 mcg/kg/min) produced no additional benefit in decreasing blood pressure; heart rate was significantly elevated at 3.2 mcg/kg/min.[3] **Diuresis during/after cardiopulmonary bypass (neonates and infants):** 0.05–0.3 mcg/kg/min titrated over 24 hours to a maximum dose of 1 mcg/kg/min has been given for 1–15 days in neonates unresponsive to conventional diuretic therapy; urine output (UOP) increased from 3.6 to 5.8 mL/kg/hr.[4] Another study found a reduction in diuretic and vasodilator use when 1 mcg/kg/min was administered to infants during bypass.[5] Conversely, 0.1 mcg/kg/min during surgery and continued for 72 hours was found to have no effect on UOP, fluid balance, or acute kidney injury incidence in neonates.[6] **Diuresis or to enhance renal perfusion in critically ill patients (0–18 years):** A retrospective study of 13 patients receiving 0.01–0.5 mcg/kg/min observed increased UOP without unfavorable adverse effects in the 24-hour period after initiating fenoldopam.[7] **Severe hypertension (children 1–17 years)[8]:** 0.2–0.8 mcg/kg/min. **Prevention of acute kidney injury:** 0.2 mcg/kg/min titrated up to 0.4 and 1.5 mcg/kg/min has been reported in two children with severe cardiomyopathy and acute kidney injury on ventricular assist devices; in one patient (8 years old), UOP increased, BUN and SCr decreased, and renal replacement therapy was avoided on 0.4 mcg/kg/min (duration of infusion 12 days). In the other patient (7 weeks old), no effect was seen with doses up to 1.5 mcg/kg/min.[9]
Dosage adjustment in organ dysfunction	No dosage adjustment necessary for renal[1,10] or hepatic dysfunction.[1]
Maximum dosage	Doses up to 4 mcg/kg/min have been given to children and up to 1.6 mcg/kg/min have been given to *adults*.[1]
Additives	Contains 1 mg/mL sodium metabisulfite and 518 mg/mL propylene glycol.[1] (See Appendix C for more specific information about potential adverse effects of sulfites and propylene glycol.)
Suitable diluents	D5W, NS.[1,11]
Maximum concentration	60 mcg/mL.[1] The manufacturer recognizes that it may be necessary to further concentrate fenoldopam solutions.[1]

Fenoldopam

Preparation and delivery	Contents of ampules must be diluted prior to administration.[1]
IV push	Not recommended.[1,11]
Intermittent infusion	Not recommended.[11]
Continuous infusion	60 mcg/mL is recommended in pediatric patients, whereas 40 mcg/mL is recommended in *adults*.[1,11] Infusion via continuous infusion pump is recommended.[1,11]
Other routes of administration	Not recommended.[1]
Comments	**Significant adverse effects:** Tachycardia and hypotension are the most commonly observed adverse events in pediatric patients. Increased intraocular pressure and hypokalemia have also been reported in *adults*.[1] **Drug interactions:** Beta blockers inhibit the sympathetic reflex response to fenoldopam and can cause unexpected hypotension; if possible, avoid concomitant use.[1] **Monitoring:** Blood pressure and heart rate should be monitored continuously, preferably intra-arterially. Serum electrolytes should be monitored.[1] **Other:** One neonate receiving fenoldopam for 48 hours after Norwood procedure acutely clotted the Blalock-Taussig shunt and required extracorporeal membrane oxygenation therapy for resuscitation; this event was thought to be potentially related to the brisk diuresis achieved.[4] A 3-year-old with glomerulonephritis status postrenal transplantation who developed severe hypertension secondary to renal failure/renal graft rejection failed to respond to 1.5 mcg/kg/min.[12]

FentaNYL Citrate

Brand names	Sublimaze, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP and ISMP reported that fentaNYL citrate was confused with SUFentanil citrate.[2,3] USP also reported that patient harm occurred.[3]
Contraindications and warnings	**Contraindications:** Patients with known intolerance to the drug.[4] **Warnings:** Only individuals trained in the use of IV anesthetics and the management of opioid respiratory effects should administer fentaNYL citrate. An opioid antagonist, intubation equipment, and oxygen should be available.[4]
Infusion-related cautions	Apnea may occur with rapid bolus injection or with large doses. Peak respiratory depression occurs 5–15 minutes after dosing. The duration of respiratory depression may be longer than the duration of analgesia.[4] Chest wall rigidity is related to high doses and rapid escalation to moderate doses; rigidity may be prevented by concomitant use of neuromuscular blocking agents with mechanical ventilation.[5–9] Neonates may be more sensitive to respiratory depressant effects and chest wall rigidity than *adults*.[7,9–11] Naloxone reverses respiratory depression[4,12] and chest wall rigidity.[7,11,12]
Dosage	**Anesthesia:** 10–100 mcg/kg/dose.[4,5,8,9,13–17] **Sedation/analgesia:** In all cases, fentaNYL doses should be titrated to clinical effect.[4,18] **Intermittent dosing** **Neonates (IV):** 1–4 mcg/kg once[19] or 0.3–3 mcg/kg[20,21] q 2–4 hr.[18] **Infants and children** **IV/IM:** 1–5 mcg/kg q 30–60 min.[12,22,23] Use lower doses for minor procedures/analgesia and higher doses for more painful procedures/analgesia/sedation requirements.[18] **Intranasal (>10 kg):** 1.5–2 mcg/kg initial dose.[24–36] Some centers limited the initial dose to a maximum of 100 mcg[36] or 180 mcg.[37] If repeat doses are needed, some centers,[24,30,37] but not all,[25,28,31,35] used a reduced dose (25% to 50% of initial dose) q 5 min PRN, up to a maximum total dose of 3 mcg/kg.[26,35] **Continuous infusion** **Neonates:** Loading dose 1–2 mcg/kg[18] followed by 0.3–5 mcg/kg/hr.[20,21,38–40] **Infants and children:** Loading dose 1–3 mcg/kg[41,42] followed by 1–3 mcg/kg/hr.[41–43] Infusions may be titrated in increments of 0.5 mcg/kg/hr.[42] **Neonates, infants and children requiring sedation/analgesia during extracorporeal membrane oxygenation (ECMO):** Loading dose 5–10 mcg/kg followed by 1–5 mcg/kg/hr (in combination with benzodiazepines) has been effective in short duration ECMO (<1 week).[44] Infusions of >20 mcg/kg/hr may be required for longer durations.[45] Tolerance may develop with continuous infusion. Increases in doses required to achieve the same effect as previously achieved with lower doses have been reported; this effect was more likely with fentaNYL infusion >5 days or cumulative fentaNYL infusion >1.6 mg/kg.[45–47]

Dosage *(cont.)*	**Patient-controlled analgesia**[48]**:** The following are recommendations for treating acute pain in opioid-naïve *adults* and children with acute pain. **Children <50 kg** **Usual starting dose (range):** 0.5–1 mcg/kg/dose (0.5–1 mcg/kg/dose). **Usual starting lockout:** 5 doses/hr; 6- to 8-minute lockout. **Usual basal or continuous rate:** 0–0.5 mcg/kg/hr. ***Adults* >50 kg** **Usual starting dose (range):** 20 mcg (10–50 mcg). **Usual starting lockout (range):** 6 minutes (5–8 minutes).
Dosage adjustment in organ dysfunction	**CrCl 10–50 mL/min/1.73 m²:** 75% of usual dose.[49] **CrCl <10 mL/min/1.73 m²:** 50% of usual dose.[49] **Patients undergoing continuous renal replacement therapy:** 75% of usual dose, titrated to effect.[49] Use with caution in hepatic impairment.[4] During ECMO, fentaNYL is sequestered by the circuit, primarily the membrane oxygenator, which may become saturated over time. Therefore, much larger doses may be required during early ECMO.[50]
Maximum dosage	75–150 mcg/kg/dose for general anesthesia.[4,51]
Additives	None.
Suitable diluents	D5W, NS.[52]
Maximum concentration	50 mcg/mL.[4]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information. **Delivery of intranasal doses:** 50-mcg/mL solution using a mucosal atomization device,[25,30,36] or using a syringe and instilling the solution drop by drop[29,32,33,35]; half of the dose per nare.
IV push	10–50 mcg/mL.[4,53] Over 3–5 minutes to reduce incidence of chest wall rigidity or respiratory depression[12,19,23]; over 1–3 minutes if given concurrently with a neuromuscular blocking agent during or in preparation for intubation/mechanical ventilation.[4,5,9,12] The ISMP and Vermont Oxford Network recommend a standard concentration of 10 mcg/mL for neonates.[53]
Intermittent infusion	10–50 mcg/mL.[4,18] Usually given IV push (slow) or continuously. The ISMP and Vermont Oxford Network recommend a standard concentration of 10 mcg/mL for neonates.[53]
Continuous infusion	10–50 mcg/mL.[4, 18] May be given by continuous IV infusion.[20,38,41,42,54] The ISMP and Vermont Oxford Network recommend a standard concentration of 10 mcg/mL for neonates.[53] Has been given as a continuous SC infusion in children weaning from prolonged sedation.[55]

FentaNYL Citrate

Other routes of administration	50–300 mcg/mL (solutions >50 mcg/mL are not commercially available in the United States) for IM,[4] SC,[55] nebulization,[56] IT,[57] or intranasal[24–37] administration.

Comments

Adverse effects: Withdrawal syndrome is associated with both dose and duration of therapy.[58] A prospective study found that a total fentaNYL dose of 1.5 mg/kg or infusion duration of 5 days were associated with >50% rate of withdrawal. Additionally, 100% of patients that received a total dose of ≥2.5 mg/kg or duration ≥9 days experienced withdrawal.[58] A smaller retrospective study found that withdrawal symptoms occurred in patients receiving shorter duration infusions (3 days).[59]

Acute dystonia occurred following combined treatment with fentaNYL and propofol.[60]

Emergence agitation following sevoflurane or desflurane anesthesia was greater with fentaNYL than with use of a preoperative caudal block or preoperative midazolam with thiopental induction.[61,62]

Cough may occur in up to 60% of patients after receiving boluses of 1 or 2 mcg/kg in preparation for ET intubation.[63]

Drug interactions: Other CNS depressants will potentiate the effects of fentaNYL citrate.[4]

Ferric Gluconate

Brand names	Ferrlecit
Medication error potential	None noted.
Contraindications and warnings	**Contraindications:** Hypersensitivity to ferric gluconate or its components, evidence of iron overload.[1]
Infusion-related cautions	Although serious hypersensitivity reactions, some fatal, have been reported[1] they have been at a much lower rate with ferric gluconate than with iron dextran products.[2–6] Typical reactions during infusions include flushing, hypotension, nausea, vomiting, and diarrhea,[2–6] which may be related to release of free iron. Premedication may not decrease the incidence of reactions.[7]
Dosage	An erythropoiesis stimulating agent should be used concurrently. **Iron deficiency in hemodialysis (chronic renal failure):** 1.5 mg/kg (≤125 mg/dose) elemental iron × eight dialysis sessions is recommended.[1,8,9] Doses of 1–5 mg/kg have been evaluated and doses >3 mg/kg have shown limited additional efficacy and potential for added toxicity.[10,11]
Dosage adjustment in organ dysfunction	No information available; however, considering the distribution characteristics of iron, there should be no dose adjustment necessary relative to liver or kidney function.
Maximum dosage	While doses >3 mg/kg have been used, they are associated with increased adverse effects.[11,12] Maximum total dose is 125 mg.[1]
Additives	Contains 9 mg benzyl alcohol/mL.[1] (See Appendix C for more specific information about benzyl alcohol toxicity in neonates.)
Suitable diluents	NS.[1] Stability in other solutions has not been evaluated and is not recommended.[1]
Maximum concentration	12.5 mg/mL.[1]
Preparation and delivery	Dilution in dextrose is not recommended.[1]
IV push	Up to 12.5 mg/min.[1] Higher infusion rates may be associated with increased adverse effects.[12]
Intermittent infusion	Over 1 hour.[1]
Continuous infusion	Not indicated.[1]

Other routes of administration	Not indicated.[1]

Comments

A reaction to one parenteral iron product does not predict a similar response to a different product nor does the lack of a reaction to a test dose predict that a hypersensitivity reaction will not occur during infusion of subsequent doses.[6,12]

Monitoring: Goal serum ferritin >100 ng/mL and transferrin saturation >20%.[8]

Pharmacokinetics: A study in pediatric hemodialysis patients determined that the area-under-the-concentration time curve (mg • hr/L) was greater in children than a comparative group of *adults.* Clearance was slower in children.[13]

Filgrastim

Brand names

Neupogen, Granulocyte Colony-Stimulating Factor, GCSF

Medication error potential

Look-alike, sound-alike drug names.

USP reports that filgrastim has been confused with sargramostim.[1] USP reports that Neupogen has been confused with Epogen, Neulasta, and Neurontin.[1] ISMP reports that Neupogen has been confused with Neumega.[2]

Contraindications and warnings

Contraindications: Individuals with known hypersensitivity to *Escherichia coli*–derived proteins, filgrastim, or any product components.[3]

Warnings: Rare cases of splenic rupture have been reported; some were fatal. Abdominal pain or shoulder tip pain that occurs during infusion should be evaluated.[3]

Infusion-related cautions

Allergic reactions occur more frequently with IV infusion and usually within 30 minutes of infusion.[3] Epinephrine, antihistamines, corticosteroids, and/or bronchodilators are usually effective in alleviating symptoms.[3]

Dosage

Consult individual protocol for complete dosing information.

Aplastic anemia: 400 mcg/m^2/day IV for 2 weeks[4] or 90 days.[5]

Bone marrow transplantation: 5–10 mcg/kg/day administered ≥24 hours after chemotherapy and ≥24 hours after bone marrow infusion until neutrophil recovery.[3] The table depicts dosing based on neutrophil response.[3]

Absolute Neutrophil Count (ANC)	Filgrastim Adjustment
If ANC >1000/mm^3 × 3 day	Reduce dose to 5 mcg/kg/day
If ANC remains >1000/mm^3 for 3 more days	Discontinue filgrastim
If ANC decreases to <1000/mm^3	Resume 5 mcg/kg/day
If ANC decreases to <1000/mm^3 while receiving 5 mcg/kg/day	Increase dose to 10 mcg/kg/day

Neutropenia following chemotherapy: 5–10 mcg/kg/day SC or IV for up to 14 days until neutrophil recovery.[6–11]

Congenital neutropenia or agranulocytosis: 5–15 mcg/kg/day SC as a single dose or divided and given BID[12] or 10–30 mcg/kg/day as an intermittent infusion up to 60 mcg/kg/day as a continuous infusion.[13]

Neutropenia and sepsis in neonates: 5–10 mcg/kg once[13–16] or twice[14,17] a day for 3–6 days.

Neutropenia/neutrophil dysfunction due to glycogen storage disease type 1b: 3–8 mcg/kg/day for up to 290 days[18] or 3–7.5 mcg/kg/day (SC) for 6–12 months.[19]

Mobilization of peripheral blood progenitor cells (PBPCs): 10–24 mcg/kg/day SC for 3–5 days before PBPC apheresis.[20–22]

Idiopathic or cyclic neutropenia: 5 mcg/kg SC once daily[11]

Dosage adjustment in organ dysfunction

None noted.

Filgrastim

Maximum dosage

Not established. Children with severe chronic neutropenia (19 months–14 years) have received 3–8 mcg/kg/day for up to 290 days.[19] Five of 20 children with severe aplastic anemia who failed to respond to 400 mcg/m^2/day were given 800 mcg/m^2/day or 1200 mcg/m^2/day for up to 2 weeks.[4]

Additives

Additive	300 mcg/ 1-mL Vial	480 mcg/ 1.6-mL Vial	300 mcg/ 0.5-mL Syringe	480 mcg/ 0.8-mL Syringe
Acetate	0.59 mg	0.94 mg	0.295 mg	0.472 mg
Sorbitol	50 mg	80 mg	25 mg	40 mg
Polysorbate 80	0.04 mg	0.064 mg	0.02 mg	0.032 mg
Sodium	0.035 mg	0.056 mg	0.0175 mg	0.028 mg

Suitable diluents

D5W.[3]

Maximum concentration

600 mcg/mL[3]

Preparation and delivery

Concentrations ≤5 mcg/mL may precipitate and are not recommended.[3] If concentration is 5–15 mcg/mL, normal human serum albumin should be added at a final concentration of 0.2% (2 mg/mL) to prevent adsorption of filgrastim to glass or plastic administration sets.[24]

Compatibility: Dilution in NS may cause precipitation.[3]

IV push

Not indicated.

Intermittent infusion

Over 15–60 minutes.[3,5,11–15]

Continuous infusion

The total daily dose may be diluted in 10–50 mL D5W and infused continuously over 24 hours by SC infusion at a rate not to exceed 10 mL/24 hr.[3,13,23] (See Comments section.)

Other routes of administration

SC as a bolus injection or continuous infusion IV.[3] Not administered IM.[3]

Comments

The use of colony-stimulating factors decreased febrile neutropenia, length of hospitalization, and number of infectious episodes but did not shorten the duration of neutropenia nor lessen treatment delays in children with acute lymphoblastic leukemia.[24]

Monitoring: A CBC including a platelet count should be obtained before initiation therapy with filgrastim and should be repeated at least twice a week during treatment.[3] Monitor hematocrit, temperature, urinalysis, and liver function tests. When the ANC is >10,000/mm^3 after the expected neutrophil nadir following chemotherapy filgrastim should be discontinued.[3]

Fluconazole

Brand names	Generic
Medication error potential	USP reports that fluconazole has been confused with flucytosine, fluoxetine, furosemide, itraconazole, metronidazole, and phenytoin sodium.[1] ISMP reports that Diflucan has been confused with Diprivan.[2] USP reports that Diflucan has been confused with diclofenac sodium, diflunisal, and Dilantin.[1]
Contraindications and warnings	**Contraindications:** Concomitant administration with other drugs known to prolong the QT interval and metabolized by CYP3A4 is contraindicated; concomitant administration with terfenadine is contraindicated in those receiving multiple fluconazole doses of 400 mg or greater.[3] (See Drug Interactions in the Comments section.) Fluconazole is contraindicated in patients with a hypersensitivity to the drug or any of its components.[3] **Warnings:** Fluconazole has been associated with rare cases of hepatotoxicity, including liver failure and death, exfoliative skin disorders that have rarely resulted in death, and rare cases of QT prolongation and torsades de pointes.[3]
Infusion-related cautions	Anaphylaxis has been reported rarely.[3]
Dosage	**Neonates** **Treatment:** 5–12 mg/kg/dose, per following schedule for dosing interval.[3–8] **≤7 days:** q 72 hr. **7–14 days:** q 48 hr. **>10–14 days:** q 24 hr. A loading dose of 10–25 mg/kg has been recommended in neonates. In pharmacokinetic studies, 12 mg/kg/day was necessary to produce therapeutic concentrations.[6,9,10] **Prophylaxis:** 3–6 mg/kg/dose; various schedules have been used, as follows: q 72 hr for 14 days, then q 48 hr for 14 days, then daily for a total of 6 weeks of prophylaxis.[11] q 72 hr for 14 days, then q 48 hr for a total of up to 4–6 weeks of prophylaxis.[12] q 48–72 hr for 7–30 days, then daily for a total of 4–6 weeks of prophylaxis.[13–15] Twice weekly dosing has also been recommended.[16] **Infants and children:** In general, 3–6 mg/kg/day is given in a single dose; may give up to 12 mg/kg/day for serious infections.[3,17] **Cryptococcal meningitis:** Initial dose of 12 mg/kg (up to 400 mg) followed by 6–12 mg/kg (up to 200–400 mg) given once daily.[3,17,18] **Immunocompromised (e.g., leukemia, bone marrow transplant):** 6–12 mg/kg given once daily.[19] **Oropharyngeal/esophageal candidiasis:** Initial dose of 6 mg/kg followed by 3 mg/kg given once daily.[3] **Systemic candidiasis:** 6–12 mg/kg (up to 400 mg) given once daily.[3,19]

Fluconazole

Dosage adjustment in organ dysfunction	Adjust dosage in patients with renal dysfunction.[3,20] The manufacturer recommends if CrCl is ≤50 mL/min, administer 50% of the normal dose.[3] Another reference recommends if CrCl is 10–50 mL/min, administer 1.5–6 mg/kg/day q 24 hr; and if CrCl is <10 mL/min, administer 1.5–6 mg/kg/day q 48 hr.[20] Following hemodialysis, patients should be given the recommended dose based on CrCl.[3] With continuous renal replacement therapy, give 6 mg/kg q 24 hr.[20] During continuous arteriovenous hemodiafiltration in an *adult*, total body clearance was similar to normal healthy volunteers.[21]
Maximum dosage	12 mg/kg/day[3,17,19] not to exceed 600 mg/day in older children and *adults*.[3] A 6-month-old with hydrocephalus and mycotic ventriculitis received 22 mg/kg/day with concomitant intraventricular administration (4 mg/24 hr).[22]
Additives	Available in glass or plastic containers in either sodium chloride or dextrose. Each mL of solution contains either 9-mg NaCl or 56-mg dextrose, depending on the diluent.[3,23]
Suitable diluents	D5W, LR.[23]
Maximum concentration	2 mg/mL.[3,23]
Preparation and delivery	For PN compatibility information, please see Appendix D.
IV push	Not recommended.[3]
Intermittent infusion	≤2 mg/mL.[3,23] Not to exceed 200 mg/hr in *adults*.[3,23]
Continuous infusion	No information available to support administration by this method.
Other routes of administration	Has been administered intraventricularly (4 mg/24 hr in an infant and 5 and 7.5 mg/24 hr and 7.5 and 10 mg/12 hr in an 18-year-old).[22]
Comments	**Significant adverse effects:** Prolonged QT interval and torsades de pointes have been reported in an 11-year-old receiving fluconazole.[24] Fluconazole prophylaxis in neonates has been associated with cholestasis.[16] **Drug interactions:** Fluconazole, a strong inhibitor for CYP2C9, a moderate inhibitor of CYP3A4, and a weak inhibitor of CYP1A2, is associated with numerous drug interactions.[3] Consult appropriate resources for dosing recommendations before combining any drug with fluconazole. **Pharmacokinetic considerations:** One pharmacokinetic study reported increased fluconazole clearance in children; the authors suggested a dose every 12 hours may be required in children 3–12 years of age in order to achieve therapeutic serum concentrations.[25]

Flumazenil

Brand names	Romazicon
Medication error potential	Look-alike, sound-alike drug names. Confusion for flumazenil with influenza virus vaccine.[1]
Contraindications and warnings	**U.S. boxed warning:** Flumazenil has been associated with seizures.[2] These occur most frequently when a benzodiazepine has been used long-term or in association with a tricyclic antidepressant overdose.[2] Practitioners should individualize the dosage of flumazenil and be prepared to manage seizures.[2] (See Rare Adverse Effects in the Comments section.) **Contraindications:** In those with a known hypersensitivity to flumazenil or benzodiazepines and in those receiving a benzodiazepine for control of a life-threatening condition (e.g., intracranial pressure [ICP] or status epilepticus). Flumazenil should not be used in those with symptoms of serious tricyclic antidepressant overdose.[2] (See Other in the Comments section.) **Other warnings:** The use of flumazenil is not recommended in patients with epilepsy who have received benzodiazepine therapy for a prolonged period. It should be used cautiously in the ICU setting because of the increased risk of unrecognized benzodiazepine dependence. Administration to diagnose benzodiazepine-induced sedation in the ICU is not recommended due to the risk of adverse events. Flumazenil should not be used until the effects of neuromuscular blockade have been fully reversed. Use cautiously in cases of mixed drug overdose because their toxic effects (e.g., convulsions and cardiac dysrhythmias) may emerge.[2]
Infusion-related cautions	To minimize pain or local inflammation, infuse through a freely running IV into a large vein.[2] Extravasation may cause local irritation.[2]
Dosage	The safety and effectiveness of flumazenil has not been established in patients <1 year of age.[2] The dose should be individualized based on patient response. **Reversal of** **Benzodiazepine-induced anesthesia or conscious sedation:** 0.01 mg/kg (up to 0.2 mg) over 15 seconds.[2–10] If the desired clinical response is not achieved within 45 seconds, give 0.01 mg/kg (up to 0.2 mg) and repeated at 60-second intervals to a maximum total dose of 0.05 mg/kg or 1 mg, whichever is smaller.[2,8] About 50% of patients require 5 doses.[2,8] A single, large dose of 0.1–0.2 mg has been used successfully.[3,11,12] Conversely, one study used smaller doses (0.002 mg/kg).[13] Another study used a loading dose of 10 mcg/kg followed by 5 mcg/kg/min until the patient awoke or until a maximum of 1 mg had been infused.[6] Some patients who regain complete consciousness may develop resedation within 19–50 minutes.[2] (See Other in the Comments section.) **Benzodiazepine overdose or ingestion:** 0.01 mg/kg; if no effect in 1–2 minutes; repeat dose q 2 min until patient responds or a total of 1 mg is given. A single dose of 0.2 mg (0.017 mg/kg) was used in a 12-kg child.[14] Initial doses have been followed by continuous infusions of 0.1–0.2 mcg/kg/min (0.004–0.01 mg/kg/hr) for up to 5 days to prevent resedation.[15–17] Infusions as large as 5 mcg/kg/min (0.3 mg/kg/hr) have been used.[6] **Neonatal apnea due to prenatal benzodiazepine exposure:** 0.02 mg/kg followed by 0.8 mcg/kg/min (0.05 mg/kg/hr) for 6 hours.[18] **Diagnostic potential** **Coma of unknown origin:** Several studies have reported successful use of flumazenil in this situation.[19–21] Forty percent of patients could provide information regarding their ingestion within about 10 minutes, which resulted in a 30% decrease in gastric lavage, urinary catheterization, and intubation.

Dosage *(cont.)*	**Diagnose of benzodiazepine-induced sedation in the ICU:** Not recommended due to the risk of adverse events.[2] The prognostic significance of a patient's failure to respond in cases confounded by metabolic disorder, traumatic injury, drugs other than benzodiazepines, or any other reasons not associated with benzodiazepine receptor occupancy is unknown.[2]
Dosage adjustment in organ dysfunction	No adjustment in renal dysfunction.[22] Flumazenil clearance is reduced to 40% to 60% in mild-to-moderate hepatic disease and to 25% in severe hepatic dysfunction. The initial dose should not be reduced, but repeat doses should be reduced or the interval prolonged in hepatic dysfunction.[2]
Maximum dosage	0.2 mg/dose up to a cumulative dose of 1 mg in infants and children.[2,11] Seventy-five percent of *adults* respond to a cumulative dose of 1–3 mg. Doses above 3 mg do not produce additional effects and no more than 3 mg should be given in any 1 hour.[2]
Additives	Contains 1.8 mg methylparabens, 0.2 mg propylparabens/mL, edetate disodium 0.01%, and acetic acid 0.01%.[23] (See Appendix C for specific information about parabens potential for toxicity.)
Suitable diluents	D5W, LR, or NS.[2,23]
Maximum concentration	0.1 mg/mL (commercially available).[2]
Preparation and delivery	**Stability:** Store at room temperature (20°C to 25°C).[2,23] Should be used within 24 hours following removal from original vial, whether admixed in an infusion solution or simply drawn into a syringe.[23]
IV push	0.1 mg/mL over 15 seconds (conscious sedation) to 30 seconds (general anesthesia).[2,23] Not to exceed 0.2 mg/min.[2]
Intermittent infusion	Not administered by this method.
Continuous infusion	Has been given by this method to prevent/minimize resedation; however, the final concentration and solution type was not provided.[6,15–17]
Other routes of administration	Undiluted flumazenil has been given rectally to seven children.[24,25] Doses ranged from 0.02–0.033 mg/kg and time to regain consciousness ranged from 3–15 minutes. No resedation was reported. It has also been given intranasally, in conjunction with naloxone, and to reverse over-sedation in a child undergoing dental restorations.[26]
Comments	**Rare adverse effects** **Seizures:** Although rare (1% to 2%), seizure activity may occur in patients (1) dependent on benzodiazepines for seizure control; (2) with severe hepatic impairment, who are physically dependent on benzodiazepines; and (3) who have ingested large doses of other drugs (mixed-drug overdose).[2] Activity has ranged from simple twitching and jerking, to single or multiple seizure events, to status epilepticus.[4] Seizures responded to reintroduction of a benzodiazepine or use of an anticonvulsant.[2,4] Because of the presence of flumazenil, larger than normal doses of benzodiazepines may be required.

Flumazenil

Comments *(cont.)*

Resedation: Due to the short duration of flumazenil, compared to some benzodiazepines, resedation may occur. This is especially true in the pediatric population. The use of flumazenil to reverse the effects of benzodiazepines used for conscious sedation was evaluated in one uncontrolled trial involving 107 pediatric patients (1–17 years).[8] Although seven patients (1–5 years) experienced resedation between 19 and 50 minutes (mean 25 minutes) after the start of flumazenil administration, none return to the baseline level of sedation.[8] Patients experiencing resedation may require repeat bolus doses or continuous infusion.

Elevation in ICP: Has been noted to increase ICP and decrease cerebral perfusion pressure in those who already have an elevated ICP; hence, should be used cautiously in those with head trauma.[4]

Monitoring: Monitor patient for return of sedation or respiratory depression for 2 hours after administration of last dose of flumazenil.[2,5,7] (See Rare Adverse Effects in the Comments section.)

Other: Symptoms of tricyclic antidepressant overdosage include motor abnormalities (e.g., twitching, rigidity, focal seizures), arrhythmias (e.g., wide QRS complexes, ventricular arrhythmias, heart block), anticholinergic effects (e.g., mydriasis, dry mucosa, hypoperistalsis), or cardiovascular collapse.[2]

Flumazenil has been reported to reverse zopiclone overdose in 17 of 20 *adult* patients.[27]

Fomepizole

Brand names

Antizol

Medication error potential

Look-alike, sound-alike drug names. Fomepizole may be confused with omeprazole.[1]

Contraindications and warnings

Contraindications: Should not be administered to patients with a documented serious hypersensitivity reaction to fomepizole or other pyrazoles.[2]

Warnings: Should not be given undiluted or by bolus injection.[2] (See Infusion-Related Cautions section.)

Infusion-related cautions

Vein irritation and phlebosclerosis can occur following rapid administration (≤5 minutes) of a solution of 25 mg/mL.[2] (See Contraindications and Warnings section.)

Dosage

Fomepizole is indicated if ethylene glycol or methanol ingestion is suspected based on patient history and/or anion gap metabolic acidosis, increased osmolar gap, visual disturbances, oxalate crystals in the urine, or a documented serum ethylene glycol or methanol concentration >20 mg/dL.[2]

Fomepizole is safer than ethanol or hemodialysis for suspected or confirmed ethylene glycol or methanol poisoning and is considered first-line therapy by the American Academy of Clinical Toxicology.[3,4] (See Comments section.)

Although safety and efficacy in pediatric patients has not been established,[2] fomepizole has been given to infants,[2,5–9] children,[7,9–16] and adolescents.[7,9]

Loading dose of 15 mg/kg over 30 minutes[2,5–8,10–12] followed by 10 mg/kg q 12 hr for 4 doses.[2,8,17] then increase to 15 mg/kg q 12 hr.[2,17] Fomepizole may be discontinued when ethylene glycol or methanol serum concentrations are <20 mg/dL and the patient is asymptomatic with a normal pH.[2,17]

Although little information is available, some advocate concurrent administration of thiamine (ethylene glycol),[10,18] pyridoxine (ethylene glycol),[10,17,18] and folic acid or folinic acid (methanol).[17,19] (See Comments section.)

Dosage adjustment in organ dysfunction

Extensively metabolized by the liver, with metabolites excreted renally.[2] Dosage adjustments in organ dysfunction have not been studied. Recommendations relative to hemodialysis[2,17]:

Beginning of hemodialysis	<6 hr since last dose: do not administer ≥6 hr since last dose: give next scheduled dose
During hemodialysis	Normal dose q 4 hr Some advocate a continuous infusion of 1–1.5 mg/kg/hr during hemodialysis.[20–22]
At completion of hemodialysis	<1 hr: Do not administer dose 1–3 hr: 50% of next scheduled dose >3 hr: Give next scheduled dose
Off hemodialysis	Administer next scheduled dose 12 hr after the last dose that was administered

Maximum dosage

15 mg/kg/dose,[2] but some have used 20 mg/kg/dose.[23]

Fomepizole

Additives	None reported.
Suitable diluents	<25 mg/mL in NS or D5W.[2]
Maximum concentration	<25 mg/mL.[2] Greater concentrations may cause vein irritation and phlebosclerosis.
Preparation and delivery	**Stability:** Solidifies in the vial at temperatures <25°C but does not affect the stability or efficacy. If solid, running the vial under warm water or holding in the hand will liquefy. Dilutes solution is stable and sterile for at least 24 hours when refrigerated or at room temperature[2]; however, it should be used within 24 hours of dilution since it does not contain a preservative.
IV push	Not recommended.[3]
Intermittent infusion	All doses (including loading dose) over 30 minutes.[2,17]
Continuous infusion	1–1.5 mg/kg/hr during hemodialysis.[20,22,23]
Other routes of administration	Although IV is preferred, one group noted that about one third of their patients receive the antidote orally.[22,24,25]
Comments	**Rare adverse effects:** Vertical nystagmus, lasting 60 minutes, has been reported within 2 hours of a single dose of 15 mg/kg of fomepizole in a 6-year-old child.[10] This adverse effect has not been reported in any other patient. Although adverse effects are rare,[26] transient elevations in alanine aminotransferase and aspartate aminotransferase have been reported.[2,17] **Monitoring:** Serum concentrations of fomepizole should be monitored. Although serum concentrations of 0.8 mg/L are required to inhibit alcohol dehydrogenase in most patients, concentrations of 8.2–24.6 mg/L are normally seen following dosing.[17] Also monitor plasma/urinary ethylene glycol or methanol levels, urinary oxalate (ethylene glycol), plasma/urinary osmolality, renal/hepatic function, serum electrolytes, arterial blood gases, and anion and osmolar gaps.[2] Hepatic enzymes and WBC counts should be monitored during treatment.[2] Acidosis and electrolyte imbalances can affect cardiac function.[2] ECG should be monitored and an EEG may be required in any patient who is comatose.[2] **Pharmacokinetics:** Unknown if the pharmacokinetics in infants and children differs from *adults*. Elimination is best characterized by Michaelis-Menten kinetics after acute doses, with saturable elimination occurring at therapeutic blood concentrations (8.2–24.6 mg/L).[2,23] It is thought that fomepizole rapidly induces its own metabolism; however, little evidence supports autoinduction.[23] After enzyme induction, elimination follows first-order kinetics. **Other:** Fomepizole does not affect existing acid but works by halting further acid production. It promotes the breakdown of formic acid (metabolite of methanol); therefore, supplemental IV 1 mg/kg q 6 hr of either folate or folinic acid (leucovorin) should be considered in those poisoned with methanol.[17,19] Thiamine (100 mg q 6 hr) and pyridoxine (1 mg/kg up to 50 mg q 6 hr) may be administered to prevent the formation of oxalic acid in those who have ingested ethylene glycol.[10,12,17]

Foscarnet Sodium

Brand names	Foscavir, generic
Medication error potential	None reported by ISMP or USP.[12]
Contraindications and warnings	**U.S. boxed warning:** Renal impairment is the major toxicity of foscarnet injection and frequent monitoring of renal function and hydration, accompanied by dose adjustment for renal function, is imperative.[3] Seizures related to alterations in electrolytes have been reported, and patients must be monitored for these changes and any potential sequelae.[3] Foscarnet is only indicated for use in immunocompromised patients with cytomegalovirus (CMV) retinitis and mucocutaneous acyclovir-resistant herpes simplex virus (HSV) infections.[3] **Contraindications:** Clinically significant hypersensitivity to foscarnet.[3] **Other warnings:** Anemia and granulocytopenia have been reported.[3]
Infusion-related cautions	Patients should be adequately hydrated prior to receiving foscarnet. Diuresis should be established prior to the first dose by administering NS or D5W; administer fluid concurrently with subsequent doses of foscarnet.[3] To avoid local irritation, administer via a vein that provides adequate blood flow for rapid dilution and distribution.[3]
Dosage	**CMV retinitis:** 180 mg/kg/day in 2–3 divided doses for 14–21 days, followed by 90–120 mg/kg once daily as maintenance.[3–7] **HSV infection resistant to acyclovir:** 80–120 mg/kg/day in 2–3 divided doses for 2–3 weeks or until the infection has resolved.[3,4,8,9] **Varicella infection resistant to acyclovir:** 80–120 mg/kg/day in 2–3 divided doses for 7–10 days or until no new lesions appear for 48 hours.[10,11] One case reported the use of 165 mg/kg/day for acyclovir-resistant Oka strain varicella infection while on chemotherapy.[12]
Dosage adjustment in organ dysfunction	Dosage adjustments are recommended for renal dysfunction.[3,4] Data is limited regarding use in patients with baseline CrCl $<$50 mL/min or SCr $>$2.8 mg/dL or in patients receiving hemodialysis or peritoneal dialysis; the manufacturer does not recommend use in these patients.[3,13] One reference suggests administering 60–80 mg/kg q 48 hr for CrCl 30–50 mL/min, 50–65 mg/kg q 48 hr for CrCl 10–29 mL/min, and use is not recommended for CrCl $<$10 mL/min.[13]
Maximum dosage	180 mg/kg/day during induction therapy.[3,4,5–7]
Additives	None.[3,14]
Suitable diluents	D5W, NS.[3,14]
Maximum concentration	12 mg/mL in NS or D5W for peripheral infusion and 24 mg/mL for central administration.[3,14]

Foscarnet Sodium

Preparation and delivery	**Stability:** Solutions prepared using D5W or NS should be stored under refrigeration and used within 24 hours.[3,14] **Compatibility:** No other drugs or supplements should be infused in the same catheter as foscarnet.[3,14] D30W, LR, and many other drugs and solutions (including PN solutions) are incompatible with foscarnet.[3,14]
IV push	Not recommended.[3,14]
Intermittent infusion	For peripheral administration, dilute with D5W or NS to a concentration of 12 mg/mL. For infusion via a central line, the solution of 24 mg/mL may be used and no dilution is required. Infuse at a rate not to exceed 60 mg/kg over 1 hour or 120 mg/kg over 2 hours.[3,14]
Continuous infusion	No information.
Other routes of administration	Not recommended.[3]
Comments	Foscarnet deposits in teeth and bone have been documented in animal studies, especially during early growth and development; deposits in bone have been reported in humans.[3] One report described successful HIV rescue therapy over 4 weeks in a 4-year-old with 90 mg/kg IV q 12 hr foscarnet in combination with IV zidovudine and oral nelfinavir and nevirapine.[15] One report described the use of ganciclovir and foscarnet concomitantly in a 9-year-old HIV patient who presented with CMV polyradiculopathy.[16] One report described the course of a 24-week premature infant with CMV-associated hemophagocytic lymphohistiocytosis being treated with 100 mg/kg/day of foscarnet after ganciclovir therapy failed.[17] One report described penile erosions secondary to foscarnet treatment for CMV in a 24-month old male after a nonrelated umbilical cord blood transplant for Hurler syndrome.[18]

Fosphenytoin

Brand names	Cerebyx
Medication error potential	Look-alike, sound-alike drug names. Cerebyx has been confused with Avelox, Celebrex, cetirizine, and Precedex.[1] Confusion with phenytoin has resulted in patient harm.[1] Confusion between the **mg/mL concentration** of fosphenytoin (50 mg PE/mL) and **total drug content per vial** (either 100 mg PE per 2-mL vial or 500 mg PE per 10-mL vial) has resulted in overdose and death.[2] To avoid confusion, the total drug content per container should be used (instead of the concentration in mg per mL) and pediatric hospitals should stock only the 2-mL vial.[3] *No order for fosphenytoin should be accepted if "PE" is omitted*.[4] (PE = phenytoin sodium equivalent.)
Contraindications and warnings	**Contraindications:** Patients with a known hypersensitivity to fosphenytoin or its ingredients or to other hydantoins (e.g., phenytoin) should not receive fosphenytoin.[5] Parenteral phenytoin effects ventricular automaticity and is contraindicated in patients with sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular block, and Adams–Stokes syndrome.[5] **Warnings:** Fosphenytoin should *always* be prescribed and dispensed PEs since doses of fosphenytoin are expressed as their PEs. Do *not* make any adjustment in the recommended doses, concentration in solutions, or rate of administration when substituting fosphenytoin for phenytoin sodium or vice versa.[5] Abrupt discontinuation of fosphenytoin may increase seizure frequency and/or precipitate status epilepticus.[5] If an allergic or hypersensitivity reaction or if a life-threatening adverse effect occurs, rapid substitution of alternative anticonvulsant may be necessary.[5] If a rash is present, an anticonvulsant *not* belonging to the hydantoin family and one structurally dissimilar should be used.[5–8] (See Comments section.) The FDA is investigating the possibility of an increased risk of serious skin reactions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) in patients given phenytoin who have the human leukocyte antigen allele HLA-B*1502.[5] This allele occurs almost exclusively in individuals with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais.[5] Until the FDA evaluation is finalized, fosphenytoin should be avoided as an alternative for carbamazepine in patients who test positive for HLA-B*1502.[5] (See Comments section.)
Infusion-related cautions	Administration of >3 mg PE/kg/min (150 mg PE/min) or doses larger than 15 mg PE/kg may lead to hypotension, bradycardia, and/or arrhythmias.[5] Vomiting, transient pruritus (groin and neck areas), tinnitus, nystagmus, somnolence, and ataxia have also occurred when faster rates or larger doses have been given.[5,9] Paresthesia and pruritus usually occur within several minutes of beginning the infusion and generally resolved within 10 minutes after completion of delivery.[3]
Dosage	*Each 75 mg of fosphenytoin sodium is metabolically converted to 50 mg of phenytoin after administration. Doses of fosphenytoin are expressed in PEs; therefore, fosphenytoin and phenytoin products can be converted directly (1 mg PE = 1 mg phenytoin).*[5] Larger doses may be required in obese patients.[10] (See Comments section.) **Acute seizure or status epilepticus** **Loading doses (assumes no previous fosphenytoin/phenytoin)** **Neonates (*few published reports in newborns; may prefer to use phenobarbital or a benzodiazepine*):** 15–24 mg PE/kg at a rate not to exceed 1–3 mg PE/kg/min[3] have resulted in total phenytoin concentrations of 10.5–34.5 mg/L (mean 21.6 mg/L) 8–12 hours after a dose.[11,12]

Dosage *(cont.)*	**Infants and children:** 15–20 mg PE/kg.[5,13,14] at a rate not to exceed 3 mg PE/kg/min[3] or 150 mg PE/min.[5] **Maintenance doses:** 4–8 mg PE/kg/day given as 2–3 doses.[5,13,14] Final maintenance dose should be individualized. Some reports have noted a failure to obtain a "therapeutic" serum concentration despite adequate doses.[13,15,16] **Post-traumatic epilepsy (see status epilepticus for dosing):** Although prophylactic phenytoin for the prevention of epilepsy following head trauma is controversial, some have reported that it reduces early post-traumatic epilepsy.[17–19] It should not be used for the prevention of late epilepsy.[17] (See Comments section.)
Dosage adjustment in organ dysfunction	Decreases in protein binding, increases in volume of distribution, and altered clearance in hepatic or renal dysfunction require dosage adjustment and unique monitoring.[5] (See Comments section.) Although several equations have been used to predict free phenytoin serum concentrations in those with low albumin or renal failure, they may over predict concentrations and are not recommended for use in children.[20]
Maximum dosage	Typically patients require <8 mg PE/kg/day from chronic dosing. One study in infants suggests that larger fosphenytoin maintenance doses (10 mg PE/kg/day) and more frequent dosing may be required.[16,21] Patients receiving medications known to increase the clearance of phenytoin may require larger doses.
Additives	There are approximately 0.0037 mmoL of phosphate in 1 PE of fosphenytoin.[3] Consider the amount of phosphate delivered in those who require phosphate restriction since hyperphosphatemia has been attributed to fosphenytoin in a 17-year-old patient with renal failure.[22]
Suitable diluents	D5W, D10W, LR, NS, ½NS, D5LR, D5½NS.[23]
Maximum concentration	25 PE/mL.[5]
Preparation and delivery	**Stability:** The product is a clear, colorless to pale yellow solution and any vials that develop particulate matter should not be used.[23] Intact vials should be refrigerated (2°C to 8°C). Storage at room temperature should not exceed 48 hours. Little or no loss of fosphenytoin sodium occurred after 30 days of frozen storage in polypropylene syringes followed by 7 days at 4°C or 25°C.[23] Thawed samples stored at 25°C were stable when returned to the freezer for an additional 7 days.[23] Stable in PVC bags for 7 days when stored at room temperature.[23] **Delivery system issues:** No loss occurred secondary to sorption to PVC containers.[23]
IV push	Not recommended.[3]
Intermittent infusion	≤25 mg PE/mL[5] at a rate of 1–3 mg PE/kg/min (maximum of 150 mg PE/min).[3,5] (See Infusion-Related Cautions section.)
Continuous infusion	Not given via this method.

Fosphenytoin

Other routes of administration

Rapidly absorbed via the IM route.[24] Doses of 15–18.7 mg PE/kg have been given to patients >6 months. Total injection volumes: infants 1–6.1 mL; children 2.6–8.7 mL; adolescents 5–12 mL.[25] Maintenance doses have been given IM for up to 4 days in volumes of 0.3–6 mL.[25] For IM administration, the quadriceps have been recommended. Although irritation may occur at the site of injection, the incidence is less than that noted with phenytoin sodium.[9,26] To minimize irritation, rotate the injection site and use multiple injection sites for large medication volumes. Has been given intraosseously to those <6 years of age.

Comments

Rare adverse effects: Anticonvulsant hypersensitivity syndrome is an acute, life-threatening, idiosyncratic reaction that has been reported in patients receiving phenytoin, phenobarbital, carbamazepine, primidone, and lamotrigine.[6–8] Symptoms generally develop within 1–12 weeks following initiation and include a classic triad of fever, rash, and lymphadenopathy.[6–8] Peripheral blood leucocytosis and eosinophilia and internal organ involvement may also be noted. Immediate discontinuation of the suspected anticonvulsant is essential for good outcome.[6–8] Cross-reactivity among the aromatic anticonvulsants has been noted; hence, these should not be used as alternative agents.[6–8]

Suicidal behavior/ideation: The incidence of this adverse effect has been noted to be greater than placebo (0.43% versus 0.24% risk) in patients receiving 11 anticonvulsants (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy for the treatment of epilepsy, psychiatric disorders, and other conditions.[5] The FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicide.

Monitoring: Continuously monitor blood pressure, respiratory function, and ECG during IV loading doses and for approximately 10–20 minutes after the end of an infusion.[5]

Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution and unbound phenytoin concentrations may be more useful.

Free phenytoin serum concentrations should be measured in newborns, in patients with renal dysfunction, or in those who are hypoalbuminemic because of decreases in protein binding, increases in volume of distribution, and altered clearance.[5,27,28] Phenytoin serum concentrations should not be measured until at least 2 hours and 4 hours after an IV and IM dose of fosphenytoin, respectively.[8,9,12]

The FDA does not recommend testing for the presence of *HLA-B*1502* prior to initiating phenytoin.[5]

Pharmacokinetics: In obese patients the loading doses should be calculated on adjusted body weight using the following equation[10]:

Dosing weight (kg) = ideal body weight (IBW) + 1.33 (measured weight – IBW). (See Appendix B.)

Children with severe, acute neurotrauma have markedly altered protein binding and phenytoin metabolism and may require larger doses and more frequent dosing.[21] Free serum phenytoin concentration should be monitored.

Drug interactions: No drugs are known to interfere with conversion of fosphenytoin to phenytoin.[5] Because phenytoin is a substrate for CYP2C9 (major), CYP2C19 (major) and CYP3A4, is a major inducer of CYP2C9, CYP2C19, CYP2B6 and CYP3A families, and is highly protein bound, it is associated with numerous drug interactions.[20] Consult appropriate resources for dosing recommendations before combining any drug with fosphenytoin or phenytoin.

Comments *(cont.)*

Laboratory interference: Fosphenytoin may cross-react with phenytoin in fluorescence polarization immunoassay (e.g., TDx/TDxFLx) and enzyme multiplied (e.g., EMIT) assays to falsely overestimate phenytoin concentrations if measured too soon after a dose of fosphenytoin. The error is dependent on serum concentrations of phenytoin/fosphenytoin, which is influenced by dose, route, rate of administration, and time of sampling relative to dosing.[5] It is recommended that phenytoin concentrations not be measured until at least 2 hours after an IV dose and 4 hours after an IM dose of fosphenytoin.[29] Blood samples should be collected in tubes containing ethylenediaminetetraacetic acid, which is an anticoagulant that minimize ex vivo conversion from fosphenytoin to phenytoin.[5]

Phenytoin may decrease serum concentrations of T4; produce artifactually low results in dexamethasone or metyrapone tests; and cause increased in serum concentrations of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase.[5]

Other: Formaldehyde is produced on conversion to phenytoin. No accumulation has been noted in *adults* and children during short-term use; however, caution is warranted in those with renal impairment.[5]

Furosemide

Brand names

Lasix

Medication error potential

Look-alike, sound-alike drug names.

ISMP reports that Lasix has been confused with Luvox.[1]

USP reports that Lasix has been confused with Lovenox and Lanoxin. Furosemide has been confused with famotidine, finasteride, fluconazole, fluoxetine, fosinopril, loperamide, and torsemide. No patient harm resulted.[2]

Contraindications and warnings

Contraindications: Patients with anuria or hypersensitivity to furosemide.[3]

Warnings: Loop diuretics used in excessive amounts may lead to profound diuresis with fluid and electrolyte losses.[3]

Patients with sulfonamide allergy may be hypersensitive to furosemide.[3]

Infusion-related cautions

Transient and permanent ototoxicity has been associated with administration rates >4 mg/min or >0.5 mg/kg/min.[3–5] (See Comments section.)

Dosage

Diuresis

Intermittent dosing

Neonates, preterm (<36 weeks gestational age): 1 mg/kg[3,6–8] q 24 hr.[9] Single doses up to 1.5 mg/kg[10] and 2 mg/kg[11] have been studied. 1 mg/kg q 12 hr × 4 doses has also been studied[12,13]; in babies with respiratory distress syndrome receiving furosemide prophylactically, the q 12 hr regimen was found to be no better than PRN dosing.[13] After doses of indomethacin for closure of patent ductus arteriosus, 1 mg/kg has shown conflicting results in placebo-controlled trials; a single dose regimen showed decreased renal adverse effects,[8] while a 3-dose regimen following each q 12 hr dose of indomethacin produced an increase in acute renal failure.[14]

Neonates, term: 0.5–2 mg/kg q 12–24 hr.[9,10,15–17] One study including neonates used 1–2 mg/kg q 4 hr following cardiac surgery.[18]

Infants and children: 0.5–2 mg/kg[3,17,19–21] q 4,[18,22] 6,[15,23,24] or 12 hours.[15] Dose may be increased by 0.25–1 mg/kg to achieve desired response.[19,22] In hemodynamically stable patients after cardiac surgery, doses of 0.25–1 mg/kg were given and titrated based on urine output (UOP) and central venous pressure measurements.[25] For medical emergencies (e.g., hyperkalemia), the typical maximum pediatric dose for patients not chronically taking loop diuretics is 20 mg,[21] and the recommended *adult* dose is 40–80 mg.[26]

Continuous infusion dosing: 0.1 mg/kg (minimum 1 mg)[22] or 1–2 mg/kg[27] bolus followed by continuous infusion of 0.05–0.4 mg/kg/hr.[18,22–25,27,28] A 24-hour study in infants found that continuous infusion resulted in a similar UOP at a lower dose than intermittent bolus doses (2.5 ± 0.3 mg/kg [n = 11] versus 6.8 ± 1.2 mg/kg [n = 15]).[18]

Alternating furosemide with ethacrynic acid may not overcome diuretic resistance.[29]

Nephrotic syndrome: 0.5–2 mg/kg with or after albumin 25% infusion.[30–37] A loading dose of 1 mg/kg followed by 0.3 mg/kg/hr for 24 hours has also been used.[30]

Dosage adjustment in organ dysfunction

Larger doses may be required in patients with renal dysfunction.[38]

During extracorporeal membrane oxygenation, 63% to 87% of the dose was adsorbed to the circuit. Saturation occurred by 30 minutes.[39]

Furosemide

Maximum dosage	The manufacturer suggests that doses should not exceed 1 mg/kg in premature neonates and 6 mg/kg in infants or children.[3] Maximum IV doses reported in neonates, infants and children have not exceeded 2 mg/kg.[11,18] In *adults* with acute renal failure, initial dose regimens up to 3 g/day have been used[38]; however, these doses have been associated with ototoxicity.[40]
Additives	Contains 0.162 mEq sodium/10 mg furosemide.[41]
Suitable diluents	D5W, NS, LR.[41]
Maximum concentration	10 mg/mL (undiluted).[3,41]
Preparation and delivery	**Stability:** The final pH of diluted furosemide must be slightly alkaline or in the neutral pH range or precipitation of furosemide may occur.[41] **Compatibility:** See Appendix D for PN compatibility information. **Photosensitivity:** Light exposure may cause discoloration. Discolored products should not be used.[41]
IV push	Over 1–2 minutes,[6,16,18,19,22] not to exceed 4 mg/min in *adults*.[3,41] Infusion at a rate not to exceed 0.5 mg/kg/min may provide protection against ototoxicity in infants and children.[42] (See Comments section.)
Intermittent infusion	The ISMP and Vermont Oxford Network recommend standard concentrations of 2 or 10 mg/mL for neonates.[43] Infusion at a rate not exceeding 0.5 mg/kg/min may provide protection against ototoxicity in infants.[42]
Continuous infusion	<10 mg/mL.[3] The ISMP and Vermont Oxford Network recommend standard concentrations of 2 and 10 mg/mL for neonates.[43] May be diluted in D5W, LR, or NS for continuous infusion.[41]
Other routes of administration	IM.[3]
Comments	**Adverse events:** Electrolyte abnormalities including hypokalemia can occur.[3] The duration of treatment is directly related to the development of sensorineural hearing loss in neonates with persistent pulmonary hypertension. Investigators point out that this may be transient; however, they suggest that infusion at a rate not exceeding 0.5 mg/kg/min may be protective.[42] Bolus administration as opposed to continuous infusion was associated with a higher incidence of permanent hearing loss in children following congenital heart surgery.[44] Premature neonates with respiratory distress syndrome may have an increased risk of persistent patent ductus arteriosus secondary to furosemide stimulation of renal production of prostaglandin E2.[45] Up to 65% of premature infants develop nephrocalcinosis following prolonged use.[5,46] About 50% of these resolve within 5–6 months of drug discontinuation[47]; however, obstructive nephrolithiasis can occur.[48] In patients requiring long-term furosemide, renal ultrasonography is warranted a few months after initiation of therapy.[49]

Furosemide

Comments *(cont.)*

In a retrospective review, furosemide was associated with an increased incidence of nephrotoxicity in patients receiving vancomycin.[50]

A case report described hyperthermia and dermal blisters in an 18-year-old female. These recurred upon rechallenge with furosemide.[51]

Monitoring: Serum potassium concentration.[3]

Drug interactions: Aminoglycosides potentiate the ototoxicity of loop diuretics.[3,52–55]

Pharmacokinetics: Furosemide is 91% to 99% protein bound. Use cautiously in jaundiced neonates at risk for kernicterus. In vitro studies have shown bilirubin displacement in pooled cord blood samples from critically ill neonates receiving furosemide.[56]

Ganciclovir Sodium

Brand names	Cytovene
Medication error potential	Look-alike, sound-alike drug names. USP reports that ganciclovir has been confused with acyclovir and valacyclovir.[1]
Contraindications and warnings	**U.S. boxed warning:** Granulocytopenia, anemia, and thrombocytopenia are possible with ganciclovir therapy.[2] **Contraindications:** Patients with hypersensitivity to ganciclovir or acyclovir.[2] **Other warnings:** Do not administer if absolute neutrophil count <500 cells/μL or platelet count is <25,000 cells/μL. Ganciclovir has been shown to impair fertility in animal studies. Because of the possible teratogenic potential, contraception should be used for an appropriate timeframe during and after therapy.[2]
Infusion-related cautions	After initial reconstitution, the solution has a pH of 11. Despite further dilution, phlebitis and/or pain may occur at infusion site, and it should be administered only into veins with adequate blood flow to permit rapid dilution and distribution.[2]
Dosage	Adequate hydration is recommended during therapy.[2] **Cytomegalovirus (CMV) prophylaxis in high-risk hosts** **Bone marrow, liver, kidney transplantation:** Variations in regimens have been reported. The most common regimens are 6–10 mg/kg/day divided q 12 hr given either the week prior to transplant or during weeks 1–2 post-transplant, then 5–6 mg/kg/day once daily 3–5 days/week for up to 100 days.[2–7] One study reported maintenance doses of 5 mg/kg/day for 3–5 days per week were well tolerated but did not prevent reactivation of CMV.[7] Another reference reported good results after treatment with 10 mg/kg/day divided q 12 hr for 14 days, then preemptive monitoring for CMV infection.[8] **Cardiac transplantation:** One reference recommends 10 mg/kg/day divided q 12 hr for 2 weeks followed by 6 mg/kg/day for 2 weeks, combined with CMV immunoglobulin therapy.[9] **Lung transplantation:** One reference gave 10 mg/kg/day divided q 12 hr for 2 weeks followed by 5 mg/kg/day for up to 5 months.[10] Another reference gave 10 mg/kg/day divided q 12 hr for 21 days, followed by 5 mg/kg/day to complete 12 weeks of therapy.[11] **CMV retinitis:** 10 mg/kg/day divided q 12 hr for 14–21 days, then 5 mg/kg/day given 7 days/week or 6 mg/kg/day given 5 days/week.[2,5] **CMV infection in allograft recipients:** 7.5–10 mg/kg/day divided q 8–12 hr for 5–47 days.[12–15] **Congenital (symptomatic) CMV infections:** 5–15 mg/kg/day divided q 12 hr in neonates and infants.[16–25] **CMV/HIV coinfection (use not established):** Three infants received 10 mg/kg/day divided q 12 hr for 2 weeks, then 5 mg/kg/day as maintenance.[26] **CMV infection in immunocompetent host:** One child (30 months old) received 10 mg/kg/day in 2 divided doses for 21 days due to a deteriorating case of primary CMV.[27]

Dosage *(cont.)*

Human herpesvirus-6 in bone marrow transplant (BMT) patients (use not established)

Prophylaxis: 10 mg/kg/day divided q 12 hr for 1 week prior to transplantation followed by 5 mg/kg/day for 120 days after transplant.[28]

Treatment: 10 mg/kg/day divided q 12 hr for 2 weeks followed by 5 mg/kg given daily or 3 times/week for 4 weeks.[28] One 7-year-old child received ganciclovir up to 24 mg/kg/day divided into 3 doses for treatment of HHV-6 encephalitis.[29] (See Maximum Dosage section.)

Dosage adjustment in organ dysfunction

Adjust dosage in patients with renal dysfunction.[2]

CrCl (mL/min)	Induction	Maintenance
≥70	5 mg/kg q 12 hr	5 mg/kg q 24 hr
50–69	2.5 mg/kg q 12 hr	2.5 mg/kg q 24 hr
25–49	2.5 mg/kg q 24 hr	1.25 mg/kg q 24 hr
10–24	1.25 mg/kg q 24 hr	0.625 mg/kg q 24 hr
<10	1.25 mg/kg 3 times/week following hemodialysis	0.625 mg/kg 3 times/week following hemodialysis

Another reference suggests the following dosing in renal dysfunction[30]

GFR (mL/min/1.73 m^2)	Induction	Maintenance
30–50	2.5 mg/kg q 24 hr	1.25 mg/kg q 24 hr
10–29	1.25 mg/kg q 24 hr	0.625 mg/kg q 24 hr
<10	1.25 mg/kg 3 times/week	0.625 mg/kg 3 times/week

Dose adjustments should also be considered in patients with hematologic toxicity. No dose adjustment is necessary with hepatic dysfunction.

Maximum dosage

15 mg/kg/day has been given to infants[22] recommended maximum dose per labeling is 10 mg/kg/day.[2] There is a published report of a 7-year-old child receiving up to 24 mg/kg/day for HHV-6, with very close therapeutic drug monitoring and renal function monitoring.[29]

Additives

46 mg sodium/500 mg ganciclovir.[2,31]

Suitable diluents

D5W, NS, R, LR.[2,31]

Maximum concentration

10 mg/mL.[2,31]

Preparation and delivery

Preparation: Reconstituted solution has a pH of 11. Therefore, avoid direct contact with skin or mucous membranes. If contact occurs, wash skin thoroughly with soap and water and rinse eyes thoroughly with plain water. Use safe handling techniques (latex gloves, protective eyewear, and other protective equipment); ganciclovir is carcinogenic and mutagenic.[2]

Stability: Reconstitute 500 mg in 10 mL of SW and then dilute to ≤10 mg/mL in suitable diluents.[2,31] BW (containing parabens) is incompatible with ganciclovir; reconstitution with BW may cause precipitation.[2,31]

Ganciclovir Sodium

Preparation and delivery *(cont.)*	Reconstituted solution in the vial is stable for 12 hours at room temperature. The further diluted solution for infusion should be refrigerated and used within 24 hours to prevent bacterial contamination.[2,31] **Compatibility:** For PN compatibility information, please see Appendix D.
IV push	Contraindicated.[2,31]
Intermittent infusion	Infuse over 1 hour.[2,31]
Continuous infusion	No information available to support administration by this method.
Other routes of administration	IM or SC injection not recommended and may result in severe tissue irritation due to high pH.[2,31]
Comments	**Significant adverse effects:** Morphological changes to the neutrophils of a 13-year-old, allogeneic BMT patient were attributed to twice-daily infusions of ganciclovir. The changes resolved within 48 hours of discontinuing the drug.[32] Decreased renal function and myelosuppression have been reported in children; renal function improved with a dose decrease.[14] **Drug interactions:** Because ganciclovir is associated with numerous drug interactions,[2] consult appropriate resources for dosing recommendations before combining any drug with ganciclovir. **Other:** IV ganciclovir may be beneficial in infants with CMV-associated cholestasis.[33,34] Ganciclovir has been used to treat CMV enterocolitis in an 8-week-old infant and protein-losing enteropathy and retinitis due to CMV in a 6-week-old infant.[35,36] It was also successfully used for CMV colitis in a 12-week-old infant.[37] Ganciclovir was used to successfully treat an immunocompetent child with CMV infection and isolated abducens nerve palsy.[38] Ganciclovir has been used in the treatment of CMV polyradiculopathy with an induction dose of 10 mg/kg/day divided q 12 hr for 10–14 days, followed by maintenance therapy of 5 mg/kg/day, 5 days per week.[39] In vivo placental transfer of ganciclovir has occurred in a premature neonate born to a woman with AIDS receiving ganciclovir therapy for CMV retinitis and pneumonitis.[40]

Gentamicin Sulfate

Brand names

Various generics

Medication error potential

Look-alike, sound-alike drug names.

ISMP's *Confused Drug Names* lists confusion with gentian violet.[1]

USP reports confusion with clindamycin, GenTeal, tobramycin, and vancomycin.[2]

Contraindications and warnings

U.S. boxed warning: Patients with impaired renal function and those receiving large doses or prolonged therapy have an increased risk for nephrotoxicity and ototoxicity (i.e., vestibular and auditory), of which ototoxicity may be irreversible.[3–5] The risk of toxicity can also be increased by prolonged elevations in serum concentrations, concurrent use of medications known to be nephro-, neuro-, or oto-toxic, dehydration, and advancing age.[3–5] Observe closely for signs or symptoms of toxicity.[3] (See Rare Adverse Effects, Monitoring, and Drug Interactions in the Comments section.)

Contraindications: Known hypersensitivity reaction to gentamicin or other aminoglycosides.[3]

Other warnings: Aminoglycosides can cause neuromuscular blockade and potentiate the effects of neuromuscular blockers.[3,6,7] If neuromuscular blockade occurs, calcium salts may reverse it.[3] (See Appendix C for specific information.)

Infusion-related cautions

Chills, fever, tachycardia, and decreased systolic blood pressure have been associated with a pyrogenic, endotoxin-like reaction following once-daily administration of gentamicin.[8,9]

Dosage

Although use has been questioned in pediatric patients, the following equation is recommended in *adult* obese patients receiving aminoglycosides.[10–12]

Dosing weight = IBW + 0.4 (TBW – IBW). (See Appendix B.)

Loading dose: Limited data are available, but some advocate an initial dose of 3–5 mg/kg in neonates and infants.[13–18]

Maintenance dose

Neonates: Many studies using various dosing methods for aminoglycosides have been reported in neonates. Most reports have based recommendations on either weight and postnatal age (PNA)[19–25] or gestational age.[16,26–41] Use of dose and interval equations based on AUC has also been recommended in the preterm neonate.[42–45] Traditional dosing (2.5 mg/kg/dose) in premature neonates has become less commonly recommended with large dose, extended interval regimens becoming accepted practice. PNA at which any of these regimens are applicable has not been well studied, but the few studies delineating a PNA have generally been ≤7 days of age.[16,23,26,27,29–32,35,37,38,42]

Based on age and weight

	<7 days	**≥7 days**	
<1200 g	**≥1200 g**	**1200–2000 g**	**>2000 g**
2.5 mg/kg q 16–24hr[19–21]	2.5 mg/kg q 12 hr[21]	2.5 mg/kg q 8–12 hr[21]	2.5 mg/kg q 8 hr[21]
OR			
5 mg/kg q 48 hr[22,23,25]	4.5–5 mg/kg q 24–48 hr[22–24]	5 mg/kg q 24 hr[22,24]	

Dosage *(cont.)*

Based on weeks gestational age (WGA)

<30 WGA	30–34 WGA	>34 WGA
2.5–3 mg/kg q 18–36 hr[35–40]	2.5–3 mg/kg q 16–24 hr[35–38,40,41]	2.5 mg/kg q 12–24 hr[35–38,40]
OR		
4–5 mg/kg q 36–48 hr[29,32–34]	4–5 mg/kg q 24–48 hr[29,33,34]	4 mg/kg q 24 hr[16,26–31]

Infants and children

Mild-to-moderate infections: Not appropriate.[21]

Severe infections: 7.5 mg/kg/day divided q 8 hr.[3,21]

Once-daily dosing outside the neonatal period: Several investigators have reported that once-daily dosing has comparable efficacy and perhaps less toxicity than classical 8–12 hour dosing.[46–56] A single dose of *aminoglycoside* has been given once daily (over 20–30 minutes) in critically ill infants and children with severe gram-negative infections,[47–49] severe pneumonia,[57] urinary tract infections,[58] bone marrow transplantation,[50] or in febrile neutropenic patients with cancer.[51–54,56] At this time, the use of once-daily dosing in infants and children is controversial.[55,57–59] The most recent edition of the *American Academy of Pediatrics Red Book: Report of the Committee on Infectious Diseases* continues to recommend 2.5 mg/kg/dose administered in multiple daily doses in all age groups and states that once-daily dosing is investigational in children.[21]

Bacterial endocarditis (treatment)[60]: Patients with endocarditis will receive a variety of primary antibiotics (e.g., cephalosporins, ampicillin, penicillin, vancomycin) that are given with or without 3 mg/kg/day of gentamicin as a single dose or divided as multiple daily doses.[60] Duration of gentamicin varies and depends on organism sensitivity and the infection of either a native or prosthetic valve. See guideline for specific recommendations.[60]

Dosage adjustment in organ dysfunction

If CrCl is between 30–50 mL/min, give a normal dose q 12–18 hr; if CrCl is 10–29 mL/min, give a normal dose q 18–24 hr, and if CrCl is <10 mL/min, give a normal dose q 48–72 hr.[61] Individualize dose based on serum concentrations, pharmacokinetic parameters, and pharmacodynamic response.

Maximum dosage

Larger doses or shorter dosing intervals of aminoglycosides are sometimes required in patients with cystic fibrosis,[62,63] major thermal burns[3] or dermal loss,[64] ascites, or in patients with febrile granulocytopenia.[51–54,56] Based on similarities between aminoglycosides, prolonged dosing interval may be required in those receiving extracorporeal membrane oxygenation.[65]

Additives

May contain sulfites and parabens.[3,66] (See Appendix C for specific information about sulfite hypersensitivity and parabens potential for toxicity.)

Suitable diluents

D5W, NS.[3,66]

Maximum concentration

Dilution in 50–100 mL is recommended for *adults*; however, the volume in children must allow for accurate measurement and administration over 30–60 minutes.[3]

Gentamicin Sulfate

Preparation and delivery	**Delivery system issues:** The mixing of gentamicin sulfate with a beta-lactam antibiotic in vitro can result in substantial inactivation of the aminoglycoside. (See Appendix C for more specific information.) **Compatibility:** See Appendix D for PN compatibility information.[67]
IV push	Not recommended. Aminoglycosides have been safely administered by rapid IV push (over 3–5 minutes[68–70]); however, ototoxicity has been associated with elevated peak serum concentrations following bolus administration in *adults*.[71]
Intermittent infusion	Over 20–30 minutes.[3]
Continuous infusion	Not recommended. Toxicity occurs more frequently, and the value of this administration method compared to intermittent infusion has not been established.[71–73]
Other routes of administration	May be administered IM.[3]
Comments	**Rare adverse effects:** Aminoglycosides accumulate in renal cortical tissue and may damage proximal tubule cells leading to oliguric renal failure. Risk of nephrotoxicity may be influenced by type of aminoglycoside, dose, duration (cumulative dose), frequency of therapy and elevated serum concentration.[3,4] It is also increased by advancing age, pre-existing renal or hepatic dysfunction, decrease renal perfusion, hypoalbuminemia, and dehydration.[3,4] Concurrent administration of nephrotoxic drugs (e.g., cisplatin, cephaloridine, kanamycin, amikacin, neomycin, polymyxin B, colistin, streptomycin, tobramycin, vancomycin) and ototoxic medications (e.g., ethacrynic acid, furosemide) may increase the risk of toxicity and should be avoided.[3] Cochlear and/or vestibular ototoxicity has been associated with all aminoglycoside antibiotics.[5] Total AUC is a better indicator of ototoxic risk than either peak or trough serum concentration.[74,75] Use cautiously with other drugs (e.g., loop diuretics, platinum-based chemotherapeutic agents) known to cause ototoxicity. Aminoglycosides may potentiate the curare-like effects on the neuromuscular junction and should be used with caution in patients with neuromuscular disorders since they may aggravate muscle weakness.[3,6] During or following gentamicin therapy, paresthesias, tetany, positive Chvostek, and Trousseau signs and mental confusion have been described in patients with hypomagnesemia, hypocalcemia, and hypokalemia.[3] Tetany and muscle weakness have been described in infants. Aminoglycosides may enhance the respiratory depressant effect of neuromuscular-blocking agents and may prolonged blockade.[3,76,77] Appropriate corrective electrolyte therapy should be initiated. Neuromuscular blockade may be reversed by administration of calcium salts.[3] **Monitoring:** Because large variability exists in patient response to therapy, individualize dosage based on serum concentrations, clinical response, and renal function. Recommended peak and trough serum gentamicin concentration are 4–12 mg/L and $<$2 mg/L, respectively. Desired peak concentrations are dependent on the site of infection. Although serum concentration monitoring has become routine practice in many institutions, not all patients may require monitoring.[78,79] **Drug interactions:** Consult appropriate resources before combining any drug with gentamicin. **Laboratory interference:** Serum concentrations may be falsely elevated when blood samples are collected through central venous Silastic catheters.[80]

Glucarpidase

Brand names	Voraxaze
Medication error potential	None reported.
Contraindications and warnings	Hypersensitivity to glucarpidase or any component.[1] Anaphylaxis has occurred in <1% of patients.[1] Methotrexate (MTX) concentrations maybe unreliable when samples are collected within 48 hours of glucarpidase administration and measured using an immunoassay.[1] (See Comments section.) Leucovorin should not be given within 2 hours before or after glucarpidase.[1] (See Leucovorin monograph.) After 48 hours, adjust leucovorin dose based on preglucarpidase MTX concentrations.[1] Continue glucarpidase with leucovorin until the MTX concentration has been maintained below the leucovorin treatment threshold for a minimum of 3 days.[1] Continue hydration and urinary alkalinization as indicated.[1]
Infusion-related cautions	Do not administer leucovorin 2 hours before or after glucarpidase.[1] (See Dosage section.)
Dosage	*Glucarpidase is not indicated for patients with "normal" clearance of MTX (plasma MTX concentrations within 2 standard deviations of the mean MTX excretion curve specific for the dose administered) or in those with normal or mildly impaired renal function due to potential risk of subtherapeutic exposure to MTX.*[1] **Concurrent leucovorin therapy (see Leucovorin monograph):** Glucarpidase use should be accompanied by concomitant leucovorin therapy.[1] Leucovorin should not be given 2 hours before or after a glucarpidase dose since leucovorin is a substrate for glucarpidase and may compete with MTX for binding sites.[1] Continue to adjust leucovorin dose based on preglucarpidase MTX concentrations and continue to administer for the first 48 hours. Continue for at least 3 days after the MTX concentration is below the leucovorin treatment threshold.[1,2] Hydration and urinary alkalinization should also be continued with glucarpidase.[1,2] **MTX toxicity (serum concentration >1 µmol/L) due to renal impairment (FDA-approved in ages ≥1 month):** A single dose of 50 units/kg IV given over 5 minutes.[1,3–12] A retrospective review of 20 pediatric patients used doses between 13–65.6 units/kg.[4] Although studies have used 2 doses of 50 units/kg given 24 hours apart, or 50 units/kg q 4 hr for 3 doses in patients with a persistent MTX concentration >1 µmol/L,[13,14] the manufacturer notes that multiple doses did not achieve a rapid and sustained clinically important reduction in MTX concentration.[1] **Accidental intrathecal (IT) MTX overdose:** IT glucarpidase should be used in conjunction with immediate lumbar drainage.[14] 1000[15] or 2000[14] units, diluted in 12-mL normal saline and immediately given over 5 minutes, rapidly decreased cerebral spinal fluid MTX concentrations by >98%.[14,15]
Dosage adjustment in organ dysfunction	No adjustment needed in renal failure.[1] No recommendation for hepatic impairment.[1]
Maximum dosage	Not reported.

Glucarpidase

Additives	Each vial contains 1000 units of glucarpidase, lactose monohydrate (10 mg), Tris-HCl (0.6 mg), and zinc acetate dihydrate (0.002 mg).[1] The product does not contain preservatives and should be administered immediately after reconstitution.[1]
Suitable diluents	None reported.
Maximum concentration	1000 unit/mL.[1]
Preparation and delivery	**Preparation** **For IV administration:** Reconstitute 1000-unit vial with 1 mL of NS for injection. Roll and tilt to mix vial.[1] Do not shake.[1] Inspect vial and discard if the solution is not clear, colorless, and free of particulate matter.[1] **For IT administration (via lumbar route, ventriculostomy, Ommaya reservoir, or lumbar and ventriculostomy):** Reconstitute 2000 units with 12 mL preservative-free NS.[14] **Stability:** Do not freeze, but store intact vials at 2°C to 8°C (36°F to 46°F). Stable for 4 hours if refrigerated but should be used immediately as the product does not contain a preservative.[1]
IV push	Not recommended.[1]
Intermittent infusion	Administer as a 5-minute bolus. Flush IV line before and after bolus.[1]
Continuous infusion	Not recommended
Other routes of administration	Following accidental administration of intrathecal MTX, glucarpidase has been given by the lumbar route, ventriculostomy, Ommaya reservoir, or lumbar and ventriculostomy.[14,15] Doses (1000 units) have been administered through ventricular or lumbar catheter over 5 minutes.[15]
Comments	After glucarpidase therapy and upon resolution of renal dysfunction, high-dose MTX therapy has been successfully used provided renal function and serum MTX concentrations are monitored closely.[4] **Laboratory test:** Methotrexate concentrations maybe unreliable when samples are collected with 48 hours of glucarpidase administration.[1] An overestimation of MTX concentration is due to an inactive metabolite (DAMPA, or 4-deoxy-4-amino-N10-methylpteroic acid), which interferes with the immunoassays assay. If MTX concentration are needed within the 48-hour period, chromatographic assay must be used.[1]

Glycopyrrolate

Brand names	Robinul, generic
Medication error potential	Look-alike, sound-alike drug names. ISMP reports that Robinul has been confused with Reminyl.[1]
Contraindications and warnings	**Contraindications:** Known hypersensitivity to glycopyrrolate or product components.[2] **Warnings:** Glycopyrrolate causes decreased sweating, and children with fever, who are in environments with high temperatures or who undergo physical exercise, are at risk for development of heat prostration.[2]
Infusion-related cautions	Dysrhythmias have been reported in children.[2]
Dosage	**Preanesthetic:** Given 30–60 minutes prior to anesthesia induction or when preanesthetic narcotics and/or sedatives are given.[2–8] **Neonates:** 3–5 mcg/kg.[7,9] **Infants and children:** 4 mcg/kg; up to 9 mcg/kg may be needed for infants 1 month to 2 years old.[2–6,8] One group evaluating the effects of ondansetron on vomiting associated with ketamine sedation used 5 mcg/kg (maximum 250 mcg) for an ED procedure.[10] **Intraoperative arrhythmias (secondary to drugs or vagal reflexes):** 4 mcg/kg[2–4,6] but ≤0.1 mg as a single dose.[2] May be repeated at 2- to 3-minute intervals PRN.[2] **Reversal of neuromuscular blockade:** Glycopyrrolate may be mixed with neostigmine or pyridostigmine to minimize cardiac side effects.[2] 5–10 mcg/kg[11,12] (0.2 mg of glycopyrrolate for every 1 mg of neostigmine or 5 mg of pyridostigmine).[2]
Dosage adjustment in organ dysfunction	Patients with renal impairment have delayed elimination.[2]
Maximum dosage	The maximum single intraoperative dose is 0.1 mg.[2]
Additives	Contains benzyl alcohol 0.9% as a preservative.[2] (See Appendix C for more specific information about benzyl alcohol toxicity in neonates.)
Suitable diluents	D5W, D5½NS, D5NS, D10W, NS, R.[2]
Maximum concentration	0.2 mg/mL (undiluted).[2]
Preparation and delivery	**Compatibility:** Incompatible in LR.[2]
IV push	Slowly.[2]

Glycopyrrolate

Intermittent infusion	Over 15–20 minutes.
Continuous infusion	Not indicated.[2]
Other routes of administration	IM (dosing recommendations are the same as for IV administration).[2,13]
Comments	**Adverse effects:** A paradoxical reaction, hyperexcitability, has been noted in children who received large doses of anticholinergics.[2] One group found that glycopyrrolate 6 mcg/kg prevented the bradycardia usually seen with sevoflurane-remifentanil-based anesthesia for cardiac catheterization of children (1–36 months of age) with congenital heart disease.[14] Treatment of dexmedetomidine-induced bradycardia with 5 mcg/kg of IV glycopyrrolate effectively increased heart rate but also caused significant hypertension in one small case series.[15]

Granisetron HCl

Brand names	Kytril
Medication error potential	Look-alike, sound-alike drug names. USP reports that granisetron has been confused with ondansetron.[1]
Contraindications and warnings	**Contraindications:** Patients with hypersensitivity to the drug or its components.[2] **Warnings:** Hypersensitivity reactions may occur in patients with hypersensitivity to other 5-hydroxytryptamine 3 (5-HT3) antagonists.[2] QT prolongation has been reported with granisetron. Use with caution in patients with pre-exisiting arrhythmias, cardiac disease, receiving cardio-toxic chemotherapy, with concomitant electrolyte abnormalities, or on medications that may lead to QT prolongation.[2]
Infusion-related cautions	The data on the effect of granisetron on ECG is inconsistent. One study in 22 children receiving 40 mcg/kg infused over 30 seconds following chemotherapy for acute lymphoblastic leukemia (ALL) demonstrated transient changes on ECG but no clinical symptoms.[3] In *adults*, a 30-second or 5-minute infusion of 10 mcg/kg resulted in a statistically significant prolongation in the QTc interval; however, no clinical symptoms were reported.[4] In four of 12 *adults*, bradycardia, integral change of P-waves, junctional escape beat, and atrioventricular block occurred.[5] Doses of 80 mcg/kg or 120 mcg/kg, in single or split doses, produced no clinically significant effects on ECG, pulse rate, or blood pressure in *adults*.[6]
Dosage	**Prevention of chemotherapy-induced nausea and vomiting:** 10, 20, or 40 mcg/kg,[2,7–16] given 5[10,11]–30[7–9,12,13,17] minutes prior to chemotherapy. For breakthrough nausea and vomiting in the first 24 hours of chemotherapy, the dose can be repeated.[18] The inclusion of dexamethasone is recommended.[19] **Prevention of postoperative nausea and vomiting:** 20–40 mcg/kg as a single dose before induction of surgery, immediately before reversal of anesthesia or postoperatively, not to exceed 1 mg. Doses of 10, 20, 40, 80, or 100 mcg/kg have been compared in children.[20–23] A dose of 40 mcg/kg was more effective than a dose of 10 mcg/kg.[20] Doses of 80 or 100 mcg/kg were no more effective than 40 mcg/kg.[20,21] **Prevention of shivering during pediatric spinal anesthesia:** 10 mcg/kg given once over 5 minutes just prior to spinal puncture.[24] The combination of granisetron and dexamethasone was more effective than granisetron alone.[25,26] In *adults*, doses of 0.1, 1, and 3 mg were studied and 3 mg was no more effective than 1 mg.[2]
Dosage adjustment in organ dysfunction	No dosage adjustment is needed for renal or hepatic dysfunction.[2] Clearance is significantly decreased in hepatic impairment; however, the pharmacokinetics of granisetron are highly variable and larger doses are well tolerated.[2]
Maximum dosage	Although doses of 100 mcg/kg have been studied,[23] 40 mcg/kg is the usual maximum dose.[2,7,8]
Additives	The 4-mL multidose vials (1 mg/mL) contain benzyl alcohol.[2] (See Appendix C for specific information about benzyl alcohol toxicity in neonates.)

Granisetron HCl

Suitable diluents	D5W, D5½ NS, NS.[2,27]
Maximum concentration	Undiluted (0.1 mg/mL, preservative free, or 1 mg/mL, multidose vial).
Preparation and delivery	**Stability:** Stable for 24 hours when diluted with D5W or NS and stored at room temperature.[25] Once the multidose vial has been entered, it should be used or discarded in 30 days.[2] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Over 30 seconds (undiluted) or over 2–5 minutes.[2,10,21] A dose of 40 mcg/kg (concentration unspecified) was infused over 30 seconds in children.[3]
Intermittent infusion	Over 30 minutes.[8,9,12]
Continuous infusion	Although continuous infusion has been used in *adults*,[28] continuous infusion has not been reported in pediatric patients.
Other routes of administration	Has been given IM in *adults*.[29,30]
Comments	A decrease in effectiveness was noted with prolonged use.[13] Response appears to be best in children <6 years of age[12] and is least in girls.[13] **Pharmacokinetics:** Pharmacokinetic parameters were significantly more variable in children with ALL who were given 1–3 mg (48.6–85.7 mcg/kg) compared to *adults* with lung cancer who were given 3 mg (41.7–53.6 mcg/kg).[31]

Haloperidol Lactate

Brand names	Haldol
Medication error potential	Look-alike, sound-alike drug names. Haloperidol has been confused with hydralazine, hydromorphone, and nadolol. Haldol has been confused with Halcion, Hytrin, and nadolol. Confusion with Stadol has resulted in patient harm.[1] Do not infuse the decanoate product intravenously.
Contraindications and warnings	**U.S. boxed warning:** None related to the pediatric population.[2] **Contraindications:** Hypersensitivity to haloperidol. Patients with significant CNS depression or who are comatose from any cause.[2] Because of risk for leukopenia, neutropenia and agranulocytosis should not be given to those with bone marrow suppression.[2] **Other warnings:** Both QT prolongation and torsades de pointes were reported with IV administration in *adults*[2,3] and were more likely to occur with larger doses.[3] If haloperidol is administered intravenously, an ECG should be continuously monitored for QT prolongation and arrhythmias, and the dosage should be reduced or the drug discontinued if changes are noted.[2,4] May cause dose-dependent irreversible extrapyramidal symptoms (e.g., pseudoparkinsonism, acute dystonic reactions, akathisia, hyperpyrexia, and tardive dyskinesia).[2] These symptoms were reported in children with burns who received IV therapy.[5] Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs increases. However, the syndrome can develop after relatively brief treatment periods at small doses. Use lowest dose and shortest duration possible. Leukopenia, neutropenia, and agranulocytosis (sometimes fatal) have been reported.[2] Discontinue therapy at first signs of blood dyscrasias or if absolute neutrophil count $<1000/mm^3$. Neuroleptic malignant syndrome (NMS) has been reported and presents as hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).[2] Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.
Infusion-related cautions	IV administration is associated with a higher incidence of cardiovascular toxicity. An ECG should be continuously monitored for QT prolongation and arrhythmias.[2]
Dosage	*Injectable haloperidol is only approved by the FDA for IM injection; however, IV administration is used off-label in clinical practice. Do not infuse the decanoate product intravenously.* Use lowest dose and shortest duration possible. **Agitation and delirium in critically ill children:** 0.013–0.28 mg/kg[4–8] or 2–5 mg/dose, repeat in 1 hour.[9] For psychosis, give 2–5 mg/dose q 4–8 hr.[9] (See Infusion-Related Cautions section.)
Dosage adjustment in organ dysfunction	None reported.[2] Use with caution in patients with renal or hepatic dysfunction.[10]
Maximum dosage	0.15 mg/kg not to exceed 5 mg.[8,9]
Additives	Contains 1.8 mg of methylparaben and 0.2 mg of propylparaben per mL.[2] (See Appendix C for specific information about potential adverse effects.)

Haloperidol Lactate

Suitable diluents	D5W.[11]
Maximum concentration	5 mg/mL (undiluted).[11]
Preparation and delivery	**Stability:** Store at room temperature.[11] **Compatibility:** See Appendix D for PN compatibility information. **Photosensitivity:** Protect from light during storage.[11]
IV push	Slowly.[7] An ECG should be monitored.[2]
Intermittent infusion	An ECG should be monitored if the drug is infused IV.[2]
Continuous infusion	Has been infused continuously in *adults*.[12]
Other routes of administration	The preferred route of administration is IM.[2]
Comments	**Adverse effects:** Hypotension (especially with IV use) and dystonic reactions may occur.[2,5,8] Haloperidol may lower the seizure threshold[2] and should be used cautiously in patients with a history of epilepsy or in those receiving antiepileptic medications.[2]

Heparin Sodium

Brand names	Various manufacturers
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] ISMP and USP report that heparin has been confused with Hespan; patient harm occurred.[2,3] The USP also reports that heparin has been confused with Refludan.[3]
Contraindications and warnings	**Contraindications:** Severe thrombocytopenia, lack of appropriate monitoring techniques (full-dose heparin), and uncontrolled active bleeding except when due to disseminated intravascular coagulation.[4] **Warnings:** Heparin sodium is available in a variety of concentrations including 1000 units/mL, 5000 units/mL, 10,000 units/mL, and 20,000 units/mL. Medication errors from using a concentrated heparin solution as a catheter lock solution have resulted in fatalities in pediatric patients.[4,5] Bleeding may result from overdosage.[4,5] Neonates may be at increased risk for intracranial hemorrhage.[6] Heparin-induced thrombocytopenia, a potentially serious side effect, may occur and is not dose related.[7–9]
Infusion-related cautions	Confirm the choice of the correct heparin concentration on the vial prior to use.[4,5]
Dosage	**Dosing adjustment for obesity:** No pediatric recommendations. In *adults,* investigations have revealed that morbidly obese patients (BMI ≥40 kg/m^2) required lower infusion rates based on actual body weight compared to nonobese patients.[10] Another study in *adults* suggested using a calculated dosing weight based on either of the following two equations, where DW = dosing weight, IBW = ideal body weight, and ABW = actual body weight: DW = IBW + 0.3 (ABW – IBW), or DW = IBW + 0.4 (ABW – IBW) **Systemic heparinization for thromboembolic disease**[5,8,11–13] **(see Infusion-Related Cautions section)** **Loading dose:** 75 units/kg IV over 10 minutes; obtain blood for activated partial thromboplastin time (aPTT) 4 hours after loading dose. **Initial maintenance dose** **Infants <1 year:** 28 units/kg/hr. **Children >1 year:** 20 units/kg/hr. **Monitoring:** Measure aPTT 4 hours after every change in rate. When aPTT is in the therapeutic range, perform daily CBC and aPTT measurements.

Dosage *(cont.)*

Adjustments in infusion rate

aPTT (sec)	Bolus (units/kg)	Hold (min)	Rate Change (%)	Repeat aPTT
<50	50	0	+10%	4 hr
50–59	0	0	+10%	4 hr
60–85	0	0	0	Next day
86–95	0	0	–10%	4 hr
96–120	0	30	–10%	4 hr
>120	0	60	–15%	4 hr

Source: Adapted with permission from Michelson AD, Bovill E, Andrew M. Antithrombotic therapy in children. *Chest.* 1995;108(4S). Adjustments are based on the assumption that aPTT of 60–85 seconds correlates with an anti-Xa level of 0.35–0.7 units/mL.[8]

Neonates: Loading dose of 50 units/kg of preservative-free heparin followed by 20–35 units/kg/hr, titrated to an initial activated clotting time (ACT) of 180–250 seconds (1.5–2.5 × baseline) and to maintain plasma heparin concentrations of 0.3–0.5 unit/mL.[14] (Note that anti-Xa levels have replaced plasma heparin concentration monitoring; the therapeutic range for neonates and children has not been established by outcomes-based studies; and variability exists among different kits that measure anti-Xa levels.)[8]

Arterial thrombosis resulting in limb ischemia: In infants <2 years, a loading dose of 75 units/kg followed by 25 units/kg/hr titrated to aPTT 80–100 seconds has been recommended.[15] The loading dose may be withheld in patients with increased risk of bleeding.

Cardiac catheterization: Current evidence-based guidelines recommend 100 units/kg initial bolus; for prolonged cases, additional boluses are suggested.[8,16,17] One study found 50 unit/kg bolus to be equally as effective as 100 units/kg followed by 20 units/kg/hr.[16]

Catheter patency

Arterial line: 0.5–5 units/mL at rates of 0.5–2 mL/hr.[18,19] Current evidence-based guidelines recommend 0.5 unit/mL at 1 mL/hr.[8]

Peripheral IV catheter: 0.5–1 unit/mL (final concentration) added to infusate[20,21] or PN.[22,23]

Peripheral IV lock irrigation: Usually 1 mL of 10 units/mL instilled q 8 hr.[24–26] However, concentrations (10–100 units/mL), volumes (2–5 mL), and dosing intervals vary widely depending on institutional protocols.[24] Some studies suggest there is no clinical difference between 2 units/mL, 10 units/mL, and saline.[27,28]

Peripherally-inserted central [venous] catheter: 0.5 unit/kg/hr continuously.[8] In preterm neonates, heparin at 0.5 units/kg/hr (in D5W or D10W, n = 100) compared to placebo (D5W or D10W, n = 101) resulted in fewer occlusions (6% versus 31%, respectively) and more completed therapies (63% versus 42%, respectively). No difference in thrombosis (20% versus 21%) or infection (10% versus 6%) was noted.[29] In another study in preterm neonates, heparin 0.5 unit/kg/hr as part of PN solution resulted in a longer catheter survival and fewer occlusions without an increase in adverse events compared to babies receiving PN without heparin.[30] A randomized, controlled trial found that the addition of heparin 0.5 unit/mL to PN solution reduced the incidence of culture-positive, catheter-related sepsis in neonates.[31]

Nontunneled central venous catheter: In infants after cardiac surgery, prophylactic heparin 10 units/kg/hr was no more effective than placebo (D5W) in reducing catheter-related thrombi.[32]

Heparin Sodium

Dosage *(cont.)*	**Tunneled central venous catheter (flush):** Current evidence-based guidelines recommend saline or heparin flushes (no specific concentration is recommended).[8] In children with hematologic or oncologic disease who were up to 17 years of age, a 3 mL, 200 unit/mL flush twice a week resulted in fewer complications than an NS flush once a week in those with a positive-pressure-valve cap device.[33] Investigators could not rule out the possibility that more frequent flushing in the heparin group was also important. **Umbilical artery catheter:** Current evidence-based guidelines recommend 0.25–1 unit/mL infused continuously.[8,34–37] (See Comments section.) **Continuous arteriovenous hemofiltration:** Loading dose of 100 units/kg followed by 5–7 units/kg/hr was successfully used in 4 neonates.[38] **Extracorporeal membrane oxygenation (ECMO):** 50–100 units/kg at the time of cannulation followed by continuous infusion titrated to ACT 1.5 × normal.[39] Dosages higher than normal may be required due to the extracorporeal circuit or due to patient-specific factors.[39] During ECMO, heparin adsorbs onto the circuit. Up to one half of the heparin administered may be inactivated by the circuit.[40] **Promotion of fat emulsion clearance:** 1 unit/mL of infusate as continuous infusion.[41,42]
Dosage adjustment in organ dysfunction	Dosage should be titrated to the appropriate aPTT or ACT.[4,5,43] Patients with renal dysfunction may be at greater risk for hemorrhage. If CrCl $<$10 mL/min/1.73 m^2, give 50% of usual dose.[43]
Maximum dosage	Individualize dosage based on aPTT,[4,8] or in some neonatal cases, ACT.[14] Loading dose not to exceed 100 units/kg.[8] $\leq$50 units/kg/hr have been used in neonates with major vessel thrombosis.[44]
Additives	While some products are preservative- and antioxidant-free, many heparin products contain benzyl alcohol or parabens.[45] (See Appendix C for specific information about adverse effects and potential toxicity from benzyl alcohol in neonates.)
Suitable diluents	D–LR, D–R, D–S, D5NS, D5½NS, D5W, D10W, fat emulsion 10%, LR, NS, ½NS, PN, R. Consult detailed reference as some variability exists with different heparin concentrations.[45]
Maximum concentration	Undiluted solutions may be used.[5] In order to infuse the correct dose safely, the product concentration must be considered; using a less concentrated product for lower doses results in a dosage that is more accurate.
Preparation and delivery	**Preparation:** The addition of heparin to infusates requires adequate mixing to ensure that pooling of heparin does not occur.[5,45] One manufacturer recommends inverting the container $\geq$6 times.[5] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Not indicated.[5]
Intermittent infusion	Over 10 minutes.[5]
Continuous infusion	The ISMP and Vermont Oxford Network recommend a standard concentration of 0.5 unit/mL (in 0.45% NaCl) for maintaining line patency in neonates.[46]

Other routes of administration	Deep SC. Not for IM use.[5]

Comments

Pharmacokinetic considerations: Protamine sulfate reverses the effects of heparin. (See Protamine Sulfate monograph.)

Rare adverse effects: Heparin induced thrombocytopenia is reported to occur in 0% to 2.6% of pediatric patients. In these patients, heparin exposure ranged from low doses (line flushes) up to supratherapeutic doses used during cardiopulmonary bypass and hemodialysis.[8]

Other: One group of investigators concluded that the addition of heparin to fluids infused to neonates peripherally did not affect catheter life significantly.[21] A prospective, randomized controlled trial of heparin 0.7 mL of 10 unit/mL solution versus saline flush for peripheral IV patency in neonates (administered a minimum of every 8 hours) found no difference between lock solutions.[47] Similarly, a systematic review of 10 studies that met review criteria could not support the use of heparin in neonates receiving peripheral infusions.[48]

Frequent IV line flushes may result in pharmacologic doses being delivered to very low birth weight infants.

FDA alert: On October 1, 2009, the FDA alerted healthcare professionals that the USP adopted new manufacturing controls for heparin. On October 8, 2009, the reference standard for heparin products changed to the World Health Organization's International Standards (IS) unit dose definition. This is about 10% less potent than the previous USP unit. Thus, the potency of heparin products has decreased.[49]

HydrALAZINE HCl

Brand names	Apresoline, generic
Medication error potential	Look-alike, sound-alike drug names. Tall man lettering is recommended to decrease confusion between hydrALAZINE and hydroxyzine[1]; no patient harm resulted.[1] Confusion has also been reported between Apresoline and Priscoline.[1] Caution should be used in converting between oral and IV dosing as dosing errors may occur.
Contraindications and warnings	**Contraindications:** Patients with hypersensitivity to hydrALAZINE or dihydralazine.[2] Also contraindicated in (1) severe tachycardia and heart failure with a high cardiac output (e.g., thyrotoxicosis); (2) myocardial insufficiency due to mechanical obstruction (e.g., aortic or mitral stenosis or constrictive pericarditis); (3) isolated right-ventricular heart failure due to pulmonary hypertension; (4) dissecting aortic aneurysm; and (5) idiopathic systemic lupus erythematosus (SLE) and related diseases.[3] **Warnings:** Prolonged treatment (>6 months) may provoke a SLE-like syndrome. More commonly occurs in slow acetylators, females, and those with renal dysfunction.[2] If SLE or similar symptoms develop, hydrALAZINE should be discontinued unless benefit of continued therapy outweighs potential risk.[2] Can cause angina attacks and ECG changes of myocardial ischemia, so use cautiously in patients with coronary artery disease.[2] Use with caution in patients with several renal disease or cerebrovascular accident.[2]
Infusion-related cautions	May cause reflex tachycardia, headaches, flushing, and fluid retention.[4] May use adjuvant beta-blocker and/or diuretic to combat these effects.[5] Combination with beta-blocker may reduce hydrALAZINE dose requirements.[5] Average maximum decrease in blood pressure should occur within 10–80 minutes.[2] Monitor blood pressure and heart rate during and after infusion.[2] When combined with other potent IV antihypertensive agents, such as diazoxide, hypotensive episodes can be prolonged; monitor patients for several hours after a precipitous decrease in blood pressure.[2]
Dosage	*Care should be taken in converting between oral and IV dosing (2:1 conversion ratio).* **Hypertension/heart failure:** 0.1–0.5 mg/kg q 3–6 hr,[4,6–16] 1.7–3.5 mg/kg/day divided q 4–6 hr.[2,17] **Hypertensive emergency:** 0.1–0.6 mg/kg q 4–6 hr.[18] In hypertensive emergencies, blood pressure should be frequently monitored to ensure that it does not decrease too quickly.[19] One group recommended that the blood pressure decrease by one-third of the desired total blood pressure decrease within 6 hours, a further one-third decrease within the next 24–36 hours, with the final one-third decrease over the next 48–72 hours.[4] If the patient is stable, a blood pressure decrease of <25% within minutes to 1 hour followed by further decreases over the next 2–6 hours has been suggested.
Dosage adjustment in organ dysfunction	Adjust dosage in patients with renal dysfunction.[20] If CrCl is 10–50 mL/min, administer a normal dose q 8 hr.[20] If CrCl is <10 mL/min, administer a normal dose q 12–24 hr in slow acetylators and q 8–16 hr in fast acetylators.[20]
Maximum dosage	1.5 mcg/kg/min,[11,12] 2 mg/kg q 3–6 hr[11,12,15] up to 9 mg/kg/day,[21] or a dose of 20[22]–25[8,13] mg.
Additives	Contains 103.6 mg propylene glycol, 0.65 mg methylparaben, and 0.35 mg polyparaben per mL.[23] (See Appendix C for more specific information about potential adverse effects of propylene glycol and parabens.)

HydrALAZINE HCl

Suitable diluents	Does not require dilution. Should not be added to infusion solutions.[23]
Maximum concentration	20 mg/mL.[23]
Preparation and delivery	**Preparation:** HydrALAZINE should not be diluted in dextrose or other sugar-containing solutions because of the formation of hydrazones, which are associated with toxicity (e.g., headache, nausea, vomiting).[24] **Stability:** Store at controlled room temperature and protect from freezing. Refrigeration of intact containers may result in precipitation or crystallization. Use immediately after vial is opened. Color change occurs after dilution with most IV solutions. Color changes within 8–12 hours after admixture do not indicate loss of potency when stored at 30°C.[23] **Delivery system issues:** HydrALAZINE in NS in PVC bags has been shown to exhibit a 10% loss in 1 week at room temperature, but it did not exhibit any loss due to sorption through an infusion set over a 7-hour simulation period.[23] May discolor upon contact with metal; discolored solutions should be discarded.[2] **Photosensitivity:** Exposure to light may increase the rate of decomposition during long-term storage (more rapid decomposition in PVC containers compared to glass bottles).
IV push	20 mg/mL over 1–2 minutes in infants,[6,7,23] with a maximum rate of 5 mg/min. A 12-year-old child received 0.32 mg/kg over 2 minutes.[10]
Intermittent infusion	No information to support administration by this method.
Continuous infusion	Not generally recommended due to solution stability.[23]
Other routes of administration	0.2–0.6 mg/kg/dose may be given IM.[25]
Comments	**Significant adverse effects:** Peripheral neuritis (paresthesias, numbness, tingling) may occur. Use concomitantly with pyridoxine if symptoms develop.[2] Blood dyscrasias may occur.[2] **Monitoring:** CBCs and antinuclear antibodies (ANAs) should be measured before and periodically during therapy. Benefit over risk should be determined when beginning or continuing therapy in a patient with a positive ANA titer.[2] Acetylation is a major route of elimination. The metabolism of hydrALAZINE will be variable in fast and slow acetylators. Most patients developing SLE symptoms will be slow acetylators. If symptoms occur, consider performing appropriate laboratory studies. If tests confirmatory, discontinue use of hydrALAZINE unless potential benefit outweighs risk. **Drug interactions:** May paradoxically reduce pressor response to epinephrine.[2] Use monoamine oxidase inhibitors with caution due to potentiation of hypotensive effects.[2] Many other drugs may potentiate the hypotensive effects of hydrALAZINE. Consult appropriate resources for recommendations before combining any drug with hydrALAZINE. **Other:** In patients with normal renal function prior to therapy, hydrALAZINE may increase renal blood flow.[2]

Hydrochloric Acid (HCl)

Brand names	Various manufacturers
Medication error potential	None reported.
Contraindications and warnings	**Warnings:** HCl has sclerosing potential if used incorrectly.
Infusion-related cautions	Infusion of 0.1 N HCl through a peripheral line results in pain at the injection site and may cause thrombophlebitis.[1] Infusion via a large vein or central venous line is preferred.[2,3]
Dosage	**Central venous catheter occlusion:** Using a 3-mL or larger syringe (see Comments section), instill a volume of 0.1 N HCl equal to the catheter volume (0.2–2 mL) and allow it to dwell for at least 20 minutes.[4–8] Withdraw and discard HCl, and then flush the catheter with an appropriate solution. If unsuccessful, the procedure can be repeated.[4–6] **Severe metabolic alkalosis (not first-line treatment):** *HCl is indicated for hypochloremic metabolic alkalosis if NaCl or KCl are contraindicated or if correction is required quickly, such as with an arterial pH >7.55, during hepatic encephalopathy, cardiac arrhythmia, or digitalis cardiotoxicity.*[2] 0.1–0.2 mmol/kg/hr until alkalosis is corrected.[9] A 16-day-old infant with refractory metabolic alkalosis received 0.5 mmol/kg/hr for 5.5 hours, then 0.75 mmol/kg/hr for 4.5 hours, and 1 mmol/kg/hr for 4 hours.[10] 0.1 N HCl has been added to an amino acid and lipid solution and infused via peripheral vein in infants with alkalosis.[1] The amount of HCl to correct the alkalosis can be calculated using the following[11]: **Chloride deficit** mEq HCl = 0.2 L/kg × weight (kg) × [103 – observed serum Cl (mEq/L)] **Bicarbonate excess**[2,3] mEq (mmol) HCl = 0.5 L/kg × weight (kg) × [observed serum HCO_3 (mEq/L) – 24] **Base-excess** mEq HCl = 0.3 L/kg × weight (kg) × measured base excess (mEq/L) The chloride-deficit method usually results in a lower dose than the other two. The dose calculated using the chloride deficit should be infused over ≥12 hours, and the dose calculated using the bicarbonate excess or base-excess method over ≥24 hours.[11] Arterial blood gas and electrolytes should be measured every 4 hours during the infusion and therapy adjusted PRN.[3]
Dosage adjustment in organ dysfunction	No information available.
Maximum dosage	0.2 mmol/kg/hr has been recommended.[2] Rates up to 25 mEq/hr in *adults* have been reported.[3] Monitor arterial pH closely during therapy and discontinue HCl when alkalosis has been corrected.
Additives	None reported. 0.1 N HCl provides 0.1 mEq/mL of hydrogen and chloride ion and has a pH of 1–1.5.
Suitable diluents	0.1 N HCl is ready for catheter instillation.

Hydrochloric Acid (HCl)

Maximum concentration	**Catheter instillation:** Usually 0.1 N HCl. In Australia, a more concentrated HCl product is commercially available and has been used as part of a protocol to treated infected catheters in children with cancer.[12] **Infusion:** Usually 0.2 N HCl[2,3]; however, a solution of 0.5 N HCl has been used via central line.[10] (See Comments section.)
Preparation and delivery	**Delivery system issues:** In an in vitro study, the surface and interior of pulmonary artery catheters infused with 0.2, 0.3, or 0.4 N HCl showed degenerative changes.[13] A subsequent in vitro study found no catheter changes following daily infusions of 0.1 N HCl for 8 weeks.[14] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	Because of the sclerosing potential, the rate of infusion should not exceed 0.2 mmol/kg/hr.[2]
Other routes of administration	Contraindicated.
Comments	The diameter of the syringe tip is inversely related to the pressure generated when pushing fluid through. Therefore, larger syringes are used to instill dwell therapies to avoid catheter rupture.[7]

Hydrocortisone Sodium Succinate

Brand names

A-HydroCort, Solu-Cortef

Medication error potential

Look-alike, sound-alike drug names.

USP reports that hydrocortisone sodium succinate has been confused with hydroxyzine hydrochloride, hydroxyzine pamoate, and methylprednisolone sodium succinate. Solu-Cortef has been confused with Solu-Medrol.[1]

Contraindications and warnings

Contraindications: Neonates (products containing benzyl alcohol), patients with systemic fungal infections, and patients with hypersensitivity to any component in the product.[2]

IM hydrocortisone is contraindicated for idiopathic thrombocytopenic purpura.[2]

Live virus (live attenuated influenza; measles, mumps, and rubella; oral polio; varicella; rotavirus; smallpox; zoster) vaccinations should not be given during treatment with immunosuppressive doses of glucocorticoids.[2] (See Drug Interactions in the Comments section.)

Warnings: Anaphylactoid reactions have been reported and those with a prior history of such reactions require appropriate precautions.[2,3]

Patients on chronic steroid therapy may require increased doses during stress.[2]

Supraphysiologic doses of corticosteroids may result in suppressed pituitary-adrenal function, so therapy of more than a few days should be decreased gradually.[2,4,5]

Immunosuppression and an increased risk for infection are possible during steroid therapy.[2] (See Adverse Effects in the Comments section.)

Infusion-related cautions

None noted.

Dosage

Doses are based on severity of disease and patient response.[2,6] The lowest dose that results in the desired effect should be used.[2,6] (See Comments section.)

Neonatal uses (preservative-free)

Bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) prevention: Although controversial, low dose hydrocortisone (1 mg/kg/day divided q 12 hr × 9 days followed by 0.5 mg/kg/day divided q 12 hr × 3 days) may increase rates of survival without BPD/CLD, especially for infants born in a setting of prenatal inflammation.[7–10]

Hypoglycemia: 5 mg/kg/day divided q 8–12 hr or 1–2 mg/kg/dose q 6 hr.[6,11]

Hypotension: 2–6 mg/kg/day divided q 6, 8, 12, or 24 hr depending on response.[12–15]

Adrenal insufficiency

Acute

Infants and young children: IV bolus of 1–2 mg/kg followed by 25–150 mg/day divided q 6–8 hr.[6] Alternatively, the AAP recommends 2–3 mg/kg (max 100 mg) followed by 1–5 mg/kg q 6 hr.[16]

Older children: IV bolus 1–2 mg/kg followed by 150–250 mg/day divided q 6–8 hr.[6] Alternatively, the AAP recommends 2–3 mg/kg (max 100 mg) followed by 12.5 mg/m^2/dose q 6 hr.[16]

Physiologic replacement: 0.25–0.35 mg/kg/day or 12–15 mg/m^2/day IM as a single dose.[5, 6]

Hydrocortisone Sodium Succinate

Dosage *(cont.)*	**Anti-inflammatory/immunosuppressive therapy:** 1–5 mg/kg/day[6] or 30–150 mg/m^2 given once a day or divided q 12 hr.[6] Children (n = 19) from 3–18 years of age with refractory rheumatoid disease were given 4 doses of 500 mg in 24 hours.[17] **Asthma:** Methylprednisolone sodium succinate is the recommended parenteral glucocorticoid for asthma.[18] The National Asthma Education and Prevention Program recommends that asthmatics (*adult*) who have received systemic corticosteroids in the past 6 months and who will undergo surgery be given 100 mg hydrocortisone q 8 hr during surgery with rapid weaning postoperatively.[18] (See Comments section.) **Congenital adrenal hyperplasia (emergency or stress dosing)[19]:** Stress dosing is encouraged in the following situations: febrile illness (temperature >38.5°C), gastroenteritis with dehydration, surgery accompanied by general anesthesia, and major trauma. **Infants and preschoolers:** Initial bolus 25 mg IV followed by 30–60 mg/m^2/day divided q 6 hr. **School-aged children:** Initial bolus 50 mg IV followed by 30–60 mg/m^2/day divided q 6 hr. **Fully grown patients:** Initial bolus 100 mg IV followed by 45–100 mg/day divided q 6 hr. **Cystic fibrosis:** 10 mg/kg/day divided q 6 hr for 10 days added to standard treatment of infants hospitalized for lower respiratory illness resulted in a greater and more sustained improvement in lung function following hospitalization.[20] **Pneumonia, community-acquired:** A case report described successful use of a bolus of 200 mg (5.7 mg/kg) followed by 10 mg/hr (7 mg/kg/day) for 5 days to treat refractory hypoxemia and severe bilateral pneumonia caused by *Streptococcus pneumoniae* in a 9-year-old girl.[21] **Septic shock:** 1–2 mg/kg/day for stress coverage up to 50 mg/kg/day as intermittent or continuous infusion(s) titrated to reversal of shock.[22] *Adult* recommendations are 50 mg q 6 hr or a bolus of 100 mg followed by 10 mg/hr. The recommended duration for *adults* is ≥7 days followed by a taper.[23]
Dosage adjustment in organ dysfunction	Those with cirrhosis of the liver or who are hypothyroid may have an exaggerated response; dose reduction may be necessary.[2] Dosing adjustment is not necessary for renal dysfunction.[24]
Maximum dosage	Not established. Use of large doses for >48–72 hours may result in hypernatremia.[2]
Additives	Contains 2.066 mEq of sodium/g.[25] May contain benzyl alcohol.[25] (See Appendix C for specific information about potential benzyl alcohol toxicity in neonates.)
Suitable diluents	D5W, D5NS, NS.[2,25]
Maximum concentration	Usually 1 mg/mL. However, 5 mg/mL in D5W was administered to 19 children without apparent adverse effects.[17] The manufacturer states that concentrations up to 60 mg/mL are acceptable in situations when a small fluid volume is desired.[2]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.
IV push	Over ≥30 seconds.[2,3]

Hydrocortisone Sodium Succinate

Intermittent infusion	Over 10 minutes[2] to 30 minutes.[17]
Continuous infusion	0.1–1 mg/mL.[6,25]
Other routes of administration	May be given IM; however, avoid injection into the deltoid muscle because of a high incidence of SC atrophy.[2]
Comments	**Adverse effects:** Musculoskeletal effects, fluid and electrolyte abnormalities, cataracts, and hyperglycemia.[2] Patients with diabetes may be at particular risk for hyperglycemia. Increased risk for immunosuppression and infection.[2] In one report, neonates who received IV hydrocortisone for refractory hypotension were more likely to develop disseminated candidal infections than those who did not.[26] Neonates receiving hydrocortisone to prevent BPD had an increased risk of GI perforation.[9] **Drug interactions:** Drugs that enhance hepatic clearance (e.g., carbamazepine, phenobarbital, phenytoin, rifampin) may decrease blood levels and lessen physiologic activity.[2] Steroids may potentiate neuromuscular blockade; monitor patients receiving concomitant nondepolarizing neuromuscular blocking agents.[6] There may be an increased risk of intestinal perforation in infants receiving concomitant prostaglandin synthesis inhibitors.[7] Live virus vaccines may be given 1 month after ending a ≥2-week course of high-dose systemic corticosteroids (2 mg/kg/day of prednisone or its equivalent, or 20 mg/day if >10 kg).[27]

Hydroxocobalamin

Brand names	Cyanokit, generic
Medication error potential	None reported by ISMP or USP.[1,2]
Contraindications and warnings	**Contraindications:** Should not be used in patients with hypersensitivity to the drug or any of its components.[3] **Warnings:** Treatment of cyanide poisoning must also include supportive emergency care, including airway management, oxygenation, hydration, cardiovascular support, and control of seizure activity.[4] Use with caution in patients with known anaphylactic reactions to hydroxocobalamin or cyanocobalamin.[4] (See Infusion-Related Cautions section.) Use will result in red discoloration of the skin and urine. Patients have also reported photosensitivity. Patient should be instructed to avoid sun exposure until the red discoloration disappears (up to 2 weeks).[4] Urine discoloration may persist for up to 5 weeks.[4] The use of folic acid alone in megaloblastic anemia due to vitamin B_{12} deficiency may result in irreversible neurologic damage.[3] The use of vitamin B_{12} alone in megaloblastic anemia due to folic acid deficiency may prevent the correct diagnosis since it will improve symptoms of folic acid deficiency.[3]
Infusion-related cautions	Allergic reactions, which may include anaphylaxis, chest tightness, edema, urticaria, pruritus, dyspnea, rash, and angioneurotic edema have occurred with hydroxocobalamin administration.[4] Increased blood pressure has occurred after initiation of the infusion, with the greatest increase occurring toward the end of the infusion.[4] Increased blood pressure was transient; a return to baseline should be expected within 4 hours of completing the infusion.[4]
Dosage	Hydroxocobalamin (vitamin B_{12}a) is a precursor to cyanocobalamin (vitamin B_{12}).[5] Two hydroxocobalamin products are available: a lyophilized powder for IV administration (25 mg/mL when reconstituted) to be used for cyanide poisoning, and a sterile solution of 1000 mcg/mL for IM administration to be used for anemias and vitamin B_{12} deficiency.[3,4] **Cyanide poisoning (hydroxocobalamin product for IV injection)**[4,5] ***Adults*:** 5 g over 15 minutes repeated once; another dose of 5 g may be given if the first doses are ineffective. **Pediatric patients:** 70 mg/kg (up to 5 g) over 30 minutes as a single infusion. **Anemia, vitamin B_{12} (hydroxocobalamin product for IM administration)**[3,5]**:** Cyanocobalamin preferred over hydroxocobalamin due to potential for antibody formation to the hydroxycobalamin-transcobalamin complex.[5] **Children with vitamin B_{12} deficiency:** 100 mcg/day for 10–15 days (total dose of 1–5 mg), then 30–60 mcg/mo maintenance has been cited.[3,5] **Schilling test:** 1000 mcg once.[5]
Dosage adjustment in organ dysfunction	No information available.
Maximum dosage	5 g in pediatric patients and 10 g in *adults*.[4] Ten *adult* patients with smoke inhalation from fire or cyanide poisoning by ingestion or inhalation have received total doses of up to 20 g; only one of the 10 survived with unspecified neurologic sequelae.[4]

Hydroxocobalamin

Additives	Hydroxocobalamin for IM administration contains 4.34% cobalt, 1.5 mg/mL methylparaben, and 0.2 mg/mL propylparaben.[3]
Suitable diluents	NS, D5W, LR (hydroxocobalamin product for IV injection).[4] Hydroxocobalamin for IM administration should not be further diluted.
Maximum concentration	25 mg/mL.[4]
Preparation and delivery	**Hydroxocobalamin product for IV injection:** Available as a single-vial kit of 5 g or two cartons of 2.5 g containing lyophilized hydroxocobalamin. Reconstitute 5-g vial with 200 mL and each 2.5-g vial with 100 mL NS (D5W or LR may be used if NS not available) using transfer spike provided in carton. Rock or rotate vial for 30–60 seconds to mix solution (do not shake). Use vented IV tubing provided in carton for infusion to patient.[4] Do not administer blood products or other drugs through the same infusion line with hydroxocobalamin.[4] Do not administer the IM product via the IV route.[3]
IV push	Not indicated.
Intermittent infusion	Infuse the IV product over 30 minutes in pediatric patients and over 15 minutes in *adults*.[4]
Continuous infusion	Not indicated.
Other routes of administration	Hydroxocobalamin for IM administration should only be administered via the IM route.[3]
Comments	**Significant adverse effects:** An acneiform rash may occur anywhere on the body within 7–28 days of administration; the rash should resolve on its own within several weeks.[4] **Monitoring:** A blood cyanide concentration is recommended by the manufacturer; however, collection of blood cyanide sample should not delay treatment.[4] Hypokalemia and thrombocytosis may occur when severe megaloblastic anemia is reversed to normal erythropoiesis by B_{12} administration; monitor potassium and platelet count closely.[3] **Laboratory interference:** Hydroxocobalamin has a dark red color, and its use may interfere with laboratory analysis with colorimetric assays (chemistry panels, hematologic and coagulation tests, and urinalysis).[4] The interference may result in increased, decreased or unpredictable concentrations and duration of interference may occur for up to 48 hours after hydroxocobalamin administration.[4] Please see manufacturer's labeling for more specific information on tests that may be affected.[4] **Other:** For cyanide poisoning, hydroxocobalamin may be advantageous over other antidotes (amyl nitrate, sodium nitrile, and sodium thiosulfate) in that it requires administration of a single antidote and does not result in methemoglobinemia. In patients with concomitant carbon monoxide poisoning, sodium thiosulfate should be added to treat the carbon monoxide poisoning.[6,7] Empiric treatment with hydroxocobalamin of cyanide toxicity secondary to smoke inhalation has been proposed.[8]

Ibandronate Sodium

Brand names	Boniva
Medication error potential	None reported.
Contraindications and warnings	**Contraindications:** Known hypersensitivity to ibandronate or to any of its excipients.[1] Uncorrected hypocalcemia.[1] **Warnings:** May cause a transient decrease in serum calcium values.[1] Osteonecrosis of the jaw has been reported in *adult* patients receiving bisphosphonates.[1] Risk factors include diagnosis of cancer, concomitant therapies (e.g., chemotherapy, radiotherapy, corticosteroids) and comorbid disorders such as anemia, coagulopathy, infection, and pre-exisiting dental disease.[1]
Infusion-related cautions	Local reactions at the injection site, such as redness or swelling, were observed infrequently. In most cases, the reaction was mild to moderate in severity.[1]
Dosage	**Osteogenesis imperfecta (OI):** Ibandronate 2 mg IV q 3 mo was compared to calcitriol PO 0.25 mcg daily for 2 years in 30 children with OI. All children also received calcium 500 mg and vitamin D 200 units daily. Children receiving ibandronate had significantly fewer new fractures and demonstrated significant increases in bone mineral density at the lumbar spine, femoral neck, trochanter, and total hip compared to calcitriol alone.[3] **Idiopathic hyperphosphatasia (IH):** 5 mg ibandronate IV was administered monthly over 2 hours to an 11-year old female with IH until alkaline phosphatase was <300 units/L. Thereafter, infusions were administered to keep alkaline phosphatase <300 units/L and were continued until skeletal maturity was reached. Deformity was prevented and hearing improved. Bone mineral density improved significantly.[4]
Dosage adjustment in organ dysfunction	Do not administer in severe renal impairment (SCr >2.3 mg/dL or CrCl <30 mL/min).[1]
Maximum dosage	6 mg.[5]
Additives	None.
Suitable diluents	Do not mix with other medications or calcium-containing solutions.[1]
Maximum concentration	Not established.
Preparation and delivery	**Preparation:** Sterile, clear, colorless, ready-to-use solution in a prefilled syringe that delivers 3.375 mg of ibandronate monosodium salt monohydrate in 3 mL of solution, equivalent to a dose of 3 mg ibandronate-free acid.[1] **Stability:** Store at controlled room temperature of 25°C (77°F).[1]
IV push	Administer over 15–30 seconds.[2]

Ibandronate Sodium

Intermittent infusion	Infuse over 1–2 hours for metastatic bone disease or for hypercalcemia of malignancy.[2,5]
Continuous infusion	Not recommended.
Other routes of administration	Not recommended.
Comments	**Monitoring:** Serum calcium levels, SCr, bone mineral density prior to initiation of therapy, and at least every 2 years.[2] **Dietary considerations:** Ensure adequate calcium and vitamin D intake; calcium supplementation should range from 800–2500 mg, depending on age and if upper limit is needed.[6] Vitamin D supplementation should range from 200–2000 International Units, depending on age and if upper limit is needed.[6]

Ibuprofen Lysine

Brand names	NeoProfen
Medication error potential	None reported.
Contraindications and warnings	**Contraindications:** Hypersensitivity to ibuprofen, any component, aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs.)[1] Neonates with (1) active bleeds (especially intracranial or GI), thrombocytopenia, or coagulation defects; (2) proven or suspected infections that are untreated; (3) impaired renal function; (4) existing or suspected necrotizing enterocolitis (NEC); and (5) congenital heart disease in whom patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow (e.g., pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta).[1] **Warnings:** Increasing BUN, creatinine, decreased glomerular filtration rate, and a small reduction in urine output (UOP) may be seen in neonates.[1] These effects are generally transient and resolve upon discontinuation of ibuprofen.[1] Ibuprofen may cause acute kidney injury especially in neonates.[1] It should be withheld in any patient with significant decreases in UOP until output returns to normal. It has been known to displace bilirubin and should be used cautiously in patients with hyperbilirubinemia.[1]
Infusion-related cautions	Avoid extravasation.[1]
Dosage	**Patent ductus arteriosus (closure of the ductus arteriosus):** The prophylactic use of ibuprofen is not currently indicated nor recommended.[2,3] *UOP should be assessed prior to each dose. If <0.6 mL/kg/hr or anuria occurs, no dose should be given until renal function normalizes.*[1] In premature infants (500–1500 g) ≤32 weeks gestational age.[1] Dose should be based on birth weight. The initial dose of 10 mg/kg should be followed by 2 doses of 5 mg/kg at 24 and 48 hours.[1,4–9] A second course of treatment, alternative pharmacologic therapy, or surgery may be needed if the ductus arteriosus fails to close or reopens following the initial course of therapy. **Other indications:** IV ibuprofen has been evaluated in *adults* for management of postoperative pain and was found to be effective and safe at a dose of 800 mg IV q 6 hr.[10]
Dosage adjustment in organ dysfunction	Should be withheld if oliguria (<0.6 mL/kg/hr) or anuria occur.[1] Avoid use in severe hepatic impairment.[11]
Maximum dosage	10 mg/kg.[1]
Additives	None reported.[1]
Suitable diluents	NS, D5W.[1,12]
Maximum concentration	17.1 mg/mL ibuprofen L-lysine (equivalent to 10 mg/mL ibuprofen); commercially available.[1,12]

Ibuprofen Lysine

Preparation and delivery	**Stability:** Use within 30 minutes of preparation. Unused contents must be discarded after first withdrawal as the product contains no preservatives.[1,12] **Compatibility:** Should not be administered concurrently with total parenteral nutrition (TPN). Stop TPN for 15 minutes before and after ibuprofen lysine administration.[1] **Photosensitivity:** Protect intact vial from light and keep in carton until use.[1,12]
IV push	Not used.
Intermittent infusion	Over 15 minutes.[1]
Continuous infusion	Not used.
Other routes of administration	None reported.[1]

Comments

Rare adverse effects

Hepatic dysfunction: In *adults,* NSAID therapy has led to liver disease.[13,14] If signs or symptoms develop, ibuprofen should be discontinued.

Intraventricular hemorrhage (IVH): Is a known complication of prematurity. Because ibuprofen may cause a transient reduction in cerebral blood flow[15,16] and is neuroprotective in animals,[9] some hypothesized that it might reduce the incidence or severity of IVH. In a large prospective study of 415 infants, 8% given ibuprofen developed severe IVH compared to 9% receiving placebo.[3] In a second study of 155 infants, grade 2 to 4 IVH developed in 16% of the ibuprofen-treated infants and 13% of the infants in the placebo group.[17]

Kernicterus: Ibuprofen lysine is about 99% bound to albumin.[1] IV ibuprofen lysine was found to be 94% to 95% protein bound in preterm newborns.[18] Ibuprofen should be used cautiously in infants with elevated total bilirubin concentrations since it may displace bilirubin from high-affinity albumin-binding sites.[1,19] One report noted possible ibuprofen-induced kernicterus in a preterm infant with hyperbilirubinemia.[20]

NEC: Although NSAIDs have the ability to reduce mesenteric blood flow,[21–24] one study reported that ibuprofen did not significantly reduce mesenteric blood flow velocity in infants.[25] The ability of NSAIDs to affect mesenteric blood flow raised concerns about its association with GI bleeding, isolated bowel perforation, and NEC in infants. While an isolated case has been reported,[26] the incidence of NEC is similar between those given ibuprofen and indomethacin.[4,7,9,27] The incidence of NEC was significantly greater in those with oliguria (21%) compared to those without (5%) oliguria.[9] A recent case report identified ibuprofen as the causative agent in a premature newborn developing GI bleeding as a complication.[28] Ibuprofen lysine appears to have little effect on platelet plug formation compared to indomethacin.[29]

Pulmonary dysfunction: Three cases of pulmonary hypertension have been reported.[30,31] A meta-analysis identified an association with ibuprofen and ~30% higher risk for chronic lung disease compared to indomethacin,[32] although another study reported no difference between ibuprofen and placebo in the development of bronchopulmonary dysplasia.[33] It appears that the need for corticosteroids for chronic lung disease may be less with oral ibuprofen.[34]

Ibuprofen Lysine

Comments *(cont.)*

Renal dysfunction: Like other NSAIDs, ibuprofen also affects renal blood flow; however, the incidence is lower than that noted with indomethacin.[4,7,9,27,35] Although it appears that oral ibuprofen may have more of an effect on renal function compared to IV ibuprofen,[36,37] preterm infants treated with IV ibuprofen experience lower SCr values, higher UOP, and less undesirable decreased organ blood flow and vasoconstrictive adverse effects than those given indomethacin.[7,9,27] In a separate study, oliguria was commonly seen with both agents within the first 3 days of treatment but resolved sooner in the ibuprofen group first.[9] Urinary PGE_2 was markedly reduced and may alter renal function in neonates in patients receiving ibuprofen.[38]

Monitoring: Renal function (SCr and BUN), UOP, CBC and platelets, liver function, and electrolytes (especially K and Na).

Oral ibuprofen appears to be as effective or more effective than IV ibuprofen for ductal closure.[34,36,37]

Drug interactions: Ibuprofen is a minor substrate of CYP2C9 and 2C19, and it is a major inhibitor of CYP2C9.[1] It is also highly protein bound to albumin. Consult appropriate resources for dosing recommendations before combining any drug with ibuprofen.

Ifosfamide

Brand names	Ifex, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1]
Contraindications and warnings	**U.S. boxed warning:** Ifosfamide should be administered under the supervision of a qualified physician. It may cause serious urotoxic effects (hemorrhagic cystitis), CNS toxicity, and severe myelosuppression.[2] (See Significant Adverse Effects in the Comments section.) **Contraindications:** Ifosfamide is contraindicated in patients with hypersensitivity to the drug, those with urinary outflow obstruction, and patients with severely depressed bone marrow.[2]
Infusion-related cautions	Hydration should accompany ifosfamide administration.[2] (See Significant Adverse Effects in the Comments section.)
Dosage	Consult individual protocols for complete dosing information. Ifosfamide is used for pediatric bone and soft tissue sarcomas, as well as Wilms tumor, neuroblastoma, and germ cell tumors. Common pediatric regimens include 1.2–1.8 g/m^2/day for 5 days q 21–28 days or 5 g/m^2/dose as a single 24-hour infusion or 3 g/m^2/day for 2 days.[3–7] High-dose therapy with 3.5 g/m^2/day for 5 days has also been used.[8]
Dosage adjustment in organ dysfunction	The dose of etoposide should be reduced by 25% in patients with CrCl $<$10 mL/min.[9] No specific guidelines exist on ifosfamide use in patients with hepatic insufficiency. However, one investigator recommended a decrease in the ifosfamide dosage by 75% in patients with an aspartate aminotransferase $>$300 units/L or a bilirubin $>$3 mg/dL.[10]
Maximum dosage	Not established.
Additives	None.
Suitable diluents	D2.5W, D5W, D5NS, NS, ½NS, LR.[2,11]
Maximum concentration	Manufacturer recommends 20 mg/mL, while another reference lists 40 mg/mL.[2,3]
Preparation and delivery	For PN compatibility information, please see Appendix D.
IV push	Not recommended.
Intermittent infusion	Dilute with SW to 50 mg/mL, then further dilute solution to a final concentration of 0.6–20 mg/mL with suitable diluents, and infuse over a minimum of 30 minutes.[2,11]

Continuous infusion

Ifosfamide has been administered as a continuous infusion.[12] Compared to intermittent administration, this route is associated with greater nephrotoxicity.[13] One paper suggested no mechanistic reason for this effect.[12]

Other routes of administration

No information available to support administration by other routes.

Comments

Significant adverse effects: Ifosfamide is a known bladder irritant. Clinical trials have shown the development of hemorrhagic cystitis in 50% of patients receiving 1.2 g/m^2 of ifosfamide.[2] Therefore, vigorous hydration (i.e., a minimum of 2 L of IV or PO fluids per day) and the uroprotectant, Mesna, are recommended in conjunction with ifosfamide administration.

Ifosfamide has been associated with severe nephrotoxicity.[3,14] Risk factors include age $<$5 years, history of cisplatin therapy, nephrectomy, renal impairment, or cumulative doses of ifosfamide $>$50–60 g/m^2.[15]

Ifosfamide is associated with a moderate (30% to 90%) risk of emesis.[16] Patients should receive antiemetic therapy to prevent acute and delayed nausea and vomiting. The recommended therapy is a 5HT3 receptor antagonist in combination with dexamethasone every day chemotherapy is administered.[16,17] These agents may be continued for up to 4 days after chemotherapy administration for the prevention of delayed nausea and vomiting. Breakthrough medications should also be offered.

Monitoring: CBC with neutrophils and platelets, urinalysis, urine output, serum electrolytes, CNS changes, liver function, and renal function.[2,3]

Drug interactions: Ifosfamide is major substrate for CYP2A6, 2C19, and 3A4, and a minor substrate for CYP2B6, 2C8, and 2C9; concomitant use with inhibitors or inducers of these CYP isoenzymes may result in drug interactions.[2,3] Consult appropriate resources for dosing recommendations before combining any drug with ifosfamide.

Imipenem–Cilastatin Sodium

Brand names

Primaxin IM, Primaxin IV

Medication error potential

Look-alike, sound-alike drug names.

USP reports confusion with ertapenem as well as confusion between Primaxin and Prevacid and Protonix.[1]

Contraindications and warnings

Contraindications: In patients with a known hypersensitivity to any component of this product or to other carbapenems or in patients who have demonstrated anaphylactic reactions to beta-lactams.[2]

Warnings

Allergic reactions: Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[2] These are more likely in patients who are sensitive to multiple allergens and in those with a history of penicillin, cephalosporins, or other beta-lactam hypersensitivity.[2–4]

Seizures: Neurotoxicity of the carbapenem antibiotics has been reported.[2] Seizures occur most commonly in patients with renal impairment and/or underlying neurologic disorders. Not recommended in pediatric patients with CNS infections because of the risk of seizures.[2] (See Rare Adverse Effects in the Comments section.)

Superinfection: Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.[2] Antibiotic use that is not directed against *C. difficile* may need to be discontinued.[2]

Infusion-related cautions

If a decision is made to give this medication to a patient with known hypersensitivity to penicillins, cephalosporins, other beta-lactams, the patient should be closely observed for allergenicity. Epinephrine, oxygen, IV steroids, and airway management may be required.

IM suspensions should *not* be given intravenously.[2]

Decrease administration rate in those who develop nausea during infusion.[2]

May cause pain at the injection site, phlebitis/thrombophlebitis, and erythema.[2]

Dosage

Neonates (limited data are available)

Postnatal age (PNA) <7 days: 40–50 mg/kg/day divided q 12 hr.[2,5,6]

PNA ≥7 days: 75 mg/kg/day divided q 8 hr.[2,5]

Infants and children

4 weeks to 3 months: 100 mg/kg/day divided q 6 hr.[2]

>3 months: 60–100 mg/kg/day divided q 6 hr.[2,5,7–10]

Up to 2 g/day[2,11] and 4 g/day[2] for moderately-susceptible organisms.

Biologic warfare or bioterrorism: The CDC and other experts recommend that treatment of inhalational anthrax spores due to biologic warfare or bioterrorism should be started on a multiple-drug parenteral regimen that includes ciprofloxacin or doxycycline and one or two additional anti-infective agents (e.g., chloramphenicol, clindamycin, rifampin, vancomycin, clarithromycin, imipenem, penicillin, or ampicillin).[12,13]

Imipenem–Cilastatin Sodium

Dosage adjustment in organ dysfunction	If CrCl is 30–50 mL/min, give 21–39 mg/kg/day divided q 8 hr[14]; if CrCl is 10–29 mL/min, give 15–25 mg/kg/day divided q 12 hr.[14] One reference suggest if the CrCl is <10 mL/min, give 7.5–12.5 mg/kg q 24 hr[14]; however, the manufacturer recommends the drug be withheld if CrCl is ≤5 mL/min unless the patient is undergoing dialysis.[2]
Maximum dosage	Although 120 mg/kg/day has been reported in a pediatric patient,[15] 90 mg/kg/day is recommended.[2] Up to 2 g/day[2] and 4 g/day in moderately susceptible infections.[2] IM dosages >1500 mg/day are not recommended.[2]
Additives	The 250- and 500-mg IV vials contain 0.8 mEq (18.8 mg) and 1.6 mEq (37.5 mg) of sodium, respectively.[16] The 500- and 750-mg IM vials contain 1.4 mEq (32 mg) and 2.1 mEq (48 mg) of sodium, respectively.[16]
Suitable diluents	D5W, D10W, NS, D5¼NS, D5½NS, D5NS, D5LR.[2,16]
Maximum concentration	5 mg/mL.[2,16]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.[17]
IV push	Not recommended.[2]
Intermittent infusion	2.5–5 mg/mL over 20–60 minutes.[2,16] The manufacturer recommends that smaller doses be infused over 20–30 minutes and that doses >500 mg be infused over 40–60 minutes.[2] Doses ≤500 mg have been infused over 15 minutes in children.[18] Infusion over at least 3 hours may be necessary to produce desirable concentrations for moderately susceptible infections in children.[19] (See Infusion-Related Cautions section.)
Continuous infusion	Not recommended.[2]
Other routes of administration	Suspension for IM administration should be reconstituted with 1% lidocaine HCl without epinephrine.[2,16] IM formulation should not be given IV and should not be used for severe or life-threatening infections (e.g., sepsis, endocarditis).[2]
Comments	**Rare adverse effects:** Neurotoxicity of the carbapenem antibiotics has been reported.[20,21] Seizures as early as the first day of therapy or after 3 days have been reported in children with meningitis. Seven of 21 pediatric patients developed seizures attributed to imipenem/cilastatin.[22] In *adults*, seizures most often occur after 7 days and appear to be related to an underlying CNS disorder, impaired renal function, and/or large doses.[23] Because of the risk of seizures, the drug should not be used in patients with CNS infections and in patients with a history of seizure disorders.[2] Use cautiously in combination with drugs that lower the seizure threshold and in patients with renal dysfunction. **Drug interactions:** Carbapenems may reduce serum valproic acid concentrations to subtherapeutic levels, resulting in loss of seizure control.[2,24] Serum valproic acid concentrations should be monitored frequently after beginning or increasing the dose of a carbapenem. Alternative antibiotics should be considered if serum valproic acid concentrations drop below the therapeutic range or a seizure occurs.[2] Because imipenem is associated with numerous drug interactions, consult appropriate resources for dosing recommendations before combining any drug with imipenem.

Immune Globulin Intravenous

Brand names

Carimune NF, Flebogamma, GAMMAGARD LIQUID, GAMMAGARD S/D, Gamunex, Octagam, Privigen

Medication error potential

Look-alike, sound-alike drug names.

USP reports that immune globulin intravenous (IGIV) has been confused with hepatitis B immune globulin.[1]

Contraindications and warnings

U.S. boxed warning: Acute renal dysfunction, acute renal failure, and death in predisposed patients have been associated with IGIV administration.[2–9] (See Comments section.)

Contraindications: Previous severe hypersensitivity reaction to immune globulin.[2–9] Those with selective immunoglobulin A (IgA) deficiency and antibodies to IgA are at risk for developing severe hypersensitivity and anaphylactic reactions.

Other warnings: Aseptic meningitis, hemolysis, transfusion-related acute lung injury, osmotic nephrosis, and thrombotic events have been reported.[2–9]

Infusion-related cautions

Patients should not be volume depleted prior to infusion.[2–8]

Inflammation reactions including facial flushing, chest tightness, chills, fever, dizziness, nausea, vomiting, diaphoresis, and hypotension may occur.[2] Infusion reactions may be attenuated by decreasing the infusion rate or stopping the infusion until the reaction subsides; then restarting at a slower rate usually decreases the severity.[2–7] One large British study found that infusion reactions occurred at a rate of 0.7% in children <10 years, which is not significantly different from the *adult* rate of 0.8%.[10]

Changing brands of IVIG may result in an increase in infusion-related reactions. Use a slower rate of infusion than usually tolerated when a change in IVIG brand is necessary. The infusion rate may be increased as the patient tolerates the change.[9]

Dosage

Primary immunodeficiency: 200–800 mg/kg/day q 3–4 wk to maintain serum immunoglobulin G (IgG) concentrations ≥400–500 mg/dL.[2–8,11,12]

Idiopathic thrombocytopenic purpura (ITP): 1–2 g/kg/day for 1–7 days initially and then PRN to maintain platelet count >30,000/mm^3.[2,5,6,11,13–16]

Kawasaki disease: A single dose of 2 g/kg is recommended over 400 mg/kg/day for 4 consecutive days.[5,16–23] Patients who have persistent fever or who have recrudescent fever after treatment may be retreated.[19,23,24]

Chronic lymphocytic leukemia: 400 mg/kg q 3–4 wk.[5]

Chronic inflammatory demyelinating polyneuropathy: Loading dose of 2 g/kg in divided doses given over 2–4 days with maintenance doses of 1 g/kg given over 1–2 days q 3 wk.[6]

Hematopoietic stem cell transplantation with severe hypogammaglobulinemia (IgG <400 mg/dL): 400 mg/kg monthly in pediatric patients and 500 mg/kg weekly in adolescents to maintain IgG ≥400 mg/dL.[25] Because the half-life is shorter in severe hypogammaglobulinemia, patients may need larger than usual doses to maintain the desired IgG concentrations.[25]

Guillain-Barré syndrome: 1 g/kg/day for 2 days or 400 mg/kg/day for 5–7 days.[16,26,27]

Other uses

Advanced HIV infection: 200–400 mg/kg q 2–4 wk.[11,28]

Hemolytic disease of the newborn: 500–1000 mg/kg/day for 1–3 days.[29–31] An increased risk of necrotizing enterocolitis has been associated with IVIG use in this population.[32–34]

Dosage *(cont.)*	**Obsessive-compulsive and tic disorder associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS):** 1 g/kg/day for 2 days resulted in significant improvements in neuropsychiatric symptoms within 1 month compared to placebo.[35] **Sepsis prevention in premature neonates:** 0.5[36–38]–1[38] g/kg at varying intervals to achieve an IgG concentration ≥700 mg/dL.[38] A large multicenter study has refuted the use of IVIG for treatment of neonatal sepsis.[39] **Sydenham chorea:** In four children who received 1 g/kg/day for 2 days, a 72% improvement in chorea severity scores was noted 1 month after treatment. The long-term response was similar to that seen with prednisone, but the response occurred more rapidly with IVIG.[40] **Toxic epidermal necrolysis/Stevens-Johnson syndrome:** Seven children received a total of 1.2–4 g/kg over up to 4 days depending on symptom improvement.[41] In a separate multicenter retrospective review that included eight children aged 4–16 years old, a total of 1.8–5.8 g/kg was given over 1–5 days.[42] These investigators recommended early IVIG treatment of 1 g/kg/day for 3 days.[42]
Dosage adjustment in organ dysfunction	No dosage adjustment may be required in renal dysfunction. However, in patients with pre-existing renal insufficiency or at risk for renal insufficiency, recommended doses should not be exceeded, the dilution should be at the minimum concentration possible, and the rate of infusion should be as slow as is practical.[9]
Maximum dosage	Typically 2 g/kg[17] but up to 5.8 g/kg has been reported.
Additives	Carimune NF contains sucrose.[2,9] Flebogamma contains polyethylene glycol and D-sorbitol.[3,9] GAMMAGARD LIQUID contains glycine.[4,9] GAMMAGARD S/D contains glycine, glucose, and polyethylene glycol.[5,9] Gamunex contains glycine.[6,9] Octagam contains maltose.[7,9] Privigen contains proline.[8,9] IgA concentrations range from trace amounts (GAMMAGARD S/D) to ≤200 mcg/mL (Octagam).[2–9] See Appendix C for more specific information about potential polyethylene glycol toxicity.
Suitable diluents	GAMMAGARD LIQUID, Gamunex, and Privigen may be diluted in D5W.[4,6,8] Lyophilized and dried concentrate products are reconstituted according to manufacturer's recommendations.[2,5]
Maximum concentration	12% (Carimune NF).[2]
Preparation and delivery	Filtration requirements for constitution and administration vary among products. Refer to manufacturer's recommendations for specific details.[2–9] **Stability:** See Appendix D for PN compatibility information.

Immune Globulin Intravenous

IV push

Not indicated.[2–9] Rapid push has been used in *adult* patients.[43]

Intermittent infusion

The rate of the infusion depends on patient tolerance.[2–9,44] Infusion reactions are more likely with the first dose; as the patient continues receiving IVIG reactions usually subside and the infusion rate may increase. (See Comments section.)

Infusion rate varies by product.[2–8] (See package insert.)

Continuous infusion

Not indicated.

Other routes of administration

Gammagard Liquid and Gamunex may be administered subcutaneously (not recommended for ITP).[4,6]

Comments

Significant adverse effects: Those at risk for acute renal dysfunction and death include those with pre-existing renal insufficiency, diabetes mellitus, >65 years of age, volume depletion, sepsis, paraproteinemia, and those receiving other nephrotoxic drugs.[2–8] Products that include sucrose are more likely to develop this toxicity.[2,3,7,8] Using the lowest concentration and the slowest infusion rate should be used in these individuals.[9]

Transient neutropenia can occur after IVIG in children with ITP.[45] A severe hemolytic anemia has been reported following infusion of high-dose IGIV for Kawasaki disease.[46]

Monitoring: Urine output, SCr, and BUN prior to initial infusion and periodically after.[2–8]

Laboratory interference: Use of products containing maltose may result in false interpretations of blood glucose readings when glucose dehydrogenase pyrroloquinoline quinone or glucose-dye-oxidoreductase based testing methods are used.[7]

Osmolality: Carimune NF reconstituted to 3% in SW is 192 mOsm/kg and to 12% in NS is 1074.[2,9] Most other products range from 240–440 mOsm/kg.[3,4,6–9]

Other: The length of time between IVIG infusion and the measles, mumps, and rubella vaccination varies according to dose as follows[47]:

IVIG Dose	Interval Before Vaccination
300–400 mg/kg	8 mo
1000 mg/kg	10 mo
1600–2000 mg/kg	11 mo

The manufacturer of Gammagard Liquid recommends delaying live attenuated vaccines by 6 months and up to 1 year for measles vaccine.[4]

Inamrinone Lactate*

Brand names	Inocor
Medication error potential	High-alert medication (antiarrhythmic) that has an increased risk of causing significant patient harm if used in error.[1]
Contraindications and warnings	**Contraindications:** Patients with a known hypersensitivity to inamrinone or bisulfites.[2] **Warnings:** Allergic-type reactions to sulfites, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, may occur in susceptible people.[2] Sulfite sensitivity is seen more frequently in individuals with asthma compared to those without asthma.[2] (See Appendix C for specific information about sulfite hypersensitivity.)
Infusion-related cautions	If hypotension occurs during the loading dose, administer 5–10 mL/kg of NS or other appropriate fluid and position the patient flat or with head down (if possible). If hypotension persists administer a vasopressor and discontinue inamrinone.[2,3]
Dosage	*Because inamrinone has been administered to only a limited number of pediatric patients, doses and side effects have not been established.*[2] *Although it has been used successfully to treat myocardial dysfunction and increased systemic or pulmonary vascular resistance, it has generally been replaced by milrinone.* **Loading dose:** Usually 0.75–1 mg/kg over 2–3 minutes.[2,4–8] May repeat 2–4 times q 15 min to a total loading dose of 3 mg/kg.[2–7] Total loading doses have ranged from 0.75–4.5 mg/kg.[2,5,9–11] **Maintenance infusion:** A six-fold variation in the pharmacokinetics of inamrinone lactate in children[2] makes it difficult to predict the optimal infusion rate; hence, dose should be titrated to effect. **Neonates:** 3–7.5 mcg/kg/min.[11,12] **Infants and children:** 2–10 mcg/kg/min.[3,11]
Dosage adjustment in organ dysfunction	If CrCl is 10–29 mL/min, give 50% of the dose, and if CrCl is <10 mL/min, give 25% of the dose.[13]
Maximum dosage	Not established. The 2010 PALS Guidelines recommend up to 10 mcg/kg/min.[3] One group administered doses up to 40 mcg/kg/min for 30 minutes in seven children who had undergone cardiac surgery.[14] This study did not show statistically significant increases in stroke volume or cardiac index at the larger doses. Total dosage (initial, supplemental doses, and cumulative infused dose) should not generally exceed 10 mg/kg/day in *adults*,[2] but doses up to 18 mg/kg/day have been infused for short periods in *adults*.[2] A 2.5-month-old infant died from accidental infusion of 180–198 mcg/kg/min.[15]
Additives	0.25 mg sodium metabisulfite per mL of inamrinone.[2] (See Appendix C for specific information about sulfite hypersensitivity.)
Suitable diluents	½NS, NS.[2]
Maximum concentration	5 mg/mL (commercially available).[2]

*Previously amrinone.

Inamrinone Lactate

Preparation and delivery	**Stability:** Use diluted solutions (1–3 mg/mL) within 24 hours.[2] **Compatibility:** Should not be diluted with solutions containing dextrose prior to injection[2] but may be administered into running dextrose infusions through a Y-Connector or directly into the tubing where preferable.[2] Furosemide should not be administered in IV lines containing inamrinone as a precipitate will form.[16] Incompatible with sodium bicarbonate.[16]
IV push	Use undiluted solution, 5 mg/mL (commercially available), over 2–3 minutes.[2] The 2010 PALS Guidelines recommend infusing over 5 minutes.[3] One group infused 0.75 mg/kg over 30 seconds.[8] Another noted that hypotension was related to the infusion rate and recommended dividing any loading dose larger than 0.75 mg/kg into two or three smaller doses.[5]
Intermittent infusion	Although concentration and solution type were not specified, a loading dose of 4.5 mg/kg has been infused over 2 hours.[10]
Continuous infusion	1–3 mg/mL in ½NS or NS.[2]
Other routes of administration	May be given IO.[3]
Comments	**Rare adverse effects:** Thrombocytopenia has been reported. In one study involving 16 children (1–134 months of age), eight developed thrombocytopenia within 19–71 hours after initiation of inamrinone lactate. When inamrinone was discontinued, thrombocytopenia resolved after 54 ± 15 hours.[7] **Drug interactions:** Because inamrinone lactate is associated with several drug–drug interactions, consult appropriate resources for dosing recommendations before combining any drug with inamrinone lactate.

Indomethacin Sodium Trihydrate

Brand names

Indocin IV

Medication error potential

None reported.

Contraindications and warnings

U.S. boxed warning: May increase the risk of cardiovascular thrombotic events, including potentially fatal myocardial infarction and stroke.[1] Risk may be increased in patients with existing cardiovascular disease and following prolonged use.[1] Is contraindicated for perioperative pain following coronary artery bypass graft surgery.[1]

Spontaneous bleeding, ulceration, and perforation of stomach or intestines may occur without warning and could be fatal. (See Rare Adverse Events in the Comments section.)

Contraindications: Hypersensitivity to indomethacin, any component, aspirin, or other nonsteroidal anti-inflammatory drugs (NSAIDs).[1] Neonates with (1) active bleeds (especially intracranial or GI), thrombocytopenia, or coagulation defects; (2) proven or suspected infections that are untreated; (3) impaired renal function; (4) existing or suspected necrotizing enterocolitis (NEC); (5) congenital heart disease in whom patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow (e.g., pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta).[1]

Other warnings: Indomethacin may suppress water excretion to a greater than sodium excretion in preterm infants leading to hyponatremia.[1]

May cause ≥50% reduction in urine output (UOP), which is accompanied by elevations of BUN and creatinine, and reductions in glomerular filtration rate and creatinine clearance.[1] These effects are generally transient and resolve upon discontinuation of indomethacin. However, indomethacin may precipitate renal insufficiency, including acute renal failure. This is especially evident in neonates with other conditions capable of adversely affecting renal function (e.g., extracellular volume depletion from any cause, congestive heart failure, sepsis, concomitant administration of nephrotoxic drugs, hepatic dysfunction). Indomethacin should be withheld in any patient with significant decreases in UOP until output returns to normal.[1]

Spontaneous intraventricular hemorrhage (IVH) is a known complication of prematurity. Because indomethacin causes platelet inhibition, it may increase the risk for IVH.[1] (See Rare Adverse Events in the Comments section.)

Infusion-related cautions

Avoid extravasation.[1]

Dosage

Patent ductus arteriosus (PDA; closure of the ductus arteriosus)

Prophylaxis (used for subclinical PDA and routine prophylaxis within 24 hours of life in very low birth weight newborns): *Prophylaxis has not been found to improve survival without neurosensory impairment.*[2–4]

0.1 mg/kg q 24 hr for 5 days[5,6]; 0.2 mg/kg q 24 hr for 5 days.[7] Continuous infusion has been used (0.004 mg/kg/hr) from 6–12 hr postnatal age (PNA) until ductus closure.[8]

Conventional treatment[9–11]

PNA at First Dose	Dose 1	Dose 2	Dose 3
<2 days	0.2 mg/kg	0.1 mg/kg	0.1 mg/kg
2–7 days	0.2 mg/kg	0.2 mg/kg	0.2 mg/kg
>7 days	0.2 mg/kg	0.25 mg/kg	0.25 mg/kg

Indomethacin Sodium Trihydrate

Dosage *(cont.)*	Assess UOP after first and second dose to determine dosing interval. If UOP is >1 mL/kg/hr, dose q 12 hr; if 0.6–1 mL/kg/hr, dose q 24 hr; if <0.6 mL/kg/hr, no dose should be given until renal function normalizes. In a study of ventilated neonates with respiratory distress syndrome, conventional doses were given every 12–18 hours.[12] Reopening of the ductus arteriosus, after a successful course of indomethacin, may require a second course of 1–3 doses using the above recommendations. If unresponsive, surgical correction may be needed.[10] **Continuous infusion:** 0.004–0.01 mg/kg/hr over 36 hours has been reported to reduce alterations in renal, cerebral, and mesenteric blood flow compared to bolus administration.[8,13,14] **Prevention of IVH:** 0.1 mg/kg q 24 hr for 3 doses beginning at 6–12 hr of age.[15–17]
Dosage adjustment in organ dysfunction	Should be withheld if oliguria (<0.6 mL/kg/hr) or anuria is present.[18]
Maximum dosage	0.25–0.4 mg/kg/dose[9,19] or cumulative 0.9–1 mg/kg in 3 days.[20,21]
Additives	None reported.
Suitable diluents	Preservative free SW or NS.[22]
Maximum concentration	1 mg/mL.[10,22]
Preparation and delivery	**Stability:** Reconstitute with 1 or 2 mL of preservative-free diluent just prior to administration. Unused portions should be immediately discarded.[10,22] However, 1 mg/mL in NS is chemically stable for 16 days at room temperature.[22] Indomethacin 0.5 mg/mL prepared with SW in the original vial was found to have little to no drug loss with refrigeration after 14 days and only 9% loss at room temperature in 10 days; when prepared under the same manner and repackaged into 1-mL polypropylene syringes, there was little to no loss reported at room temperature or refrigeration at 14 days.[22] **Compatibility:** See Appendix D for PN compatibility information. **Photosensitivity:** Protect from light.[22]
IV push	Although indomethacin has been given over 5–10 seconds,[23,24] rapid administration causes a significant decrease in mesenteric artery[25] and cerebral blood flow that may contribute to the development of NEC[25] or cerebral ischemia.[25–27]
Intermittent infusion	0.5–1 mg/mL IV over 20–30 minutes.[10,22] Do not administer via umbilical catheter vessel in superior mesenteric artery (may cause vasoconstriction and compromise intestinal blood flow); do not administer intra-arterially.[18]
Continuous infusion	Not recommended.[10]
Other routes of administration	IM administration not recommended.[10]

Indomethacin Sodium Trihydrate

Comments

Rare adverse events: A study reported a decline in coronary perfusion without major cardiac output changes following indomethacin administration in patients with hemodynamically significant PDAs. The significance of this is still unknown, but authors suggest cardiac hemodynamics be carefully monitored.[28]

IVH: Indomethacin may cause a transient reduction in cerebral blood flow.[10] Two small studies demonstrated that slower administration appears to be safer with diminished effect on cerebral blood flow; a 30-minute infusion time[29] and a 120-minute infusion time were both found to be protective.[30] In a large multicenter study, the incidence of IVH in neonates was not significantly different in neonates given indomethacin and placebo.[17] Others have reported that indomethacin may decrease the incidence and severity of IVH.[16,31]

NEC: Bleeding, with a focus on GI or NEC, has been reported with IV indomethacin regimens that consisted of 6 doses.[20,32–34] Although major GI bleeding was no more common in neonates receiving indomethacin than in those given placebo, minor GI bleeding (i.e., chemical detection of blood in the stool) was more commonly noted in those receiving indomethacin.[10]

Pulmonary dysfunction: Indomethacin appears to have less risk of chronic lung disease as compared to ibuprofen.[35]

Hepatic dysfunction: Nonsteroidal therapy in *adults* has caused liver disease.[10,36,37] If signs or symptoms develop, therapy should be discontinued.

Other affects: Hypoglycemia that developed during indomethacin therapy persisted for up to 72 hours.[38–40]

Neurological effects (dizziness, headache, and somnolence) may be attributed to the variable absorption into the CNS and rapid concentrations found in the cerebral spinal fluid.[41]

Monitoring: Renal function (SCr and BUN), UOP, CBC and platelets, serum transaminases, electrolytes (especially K and Na), and glucose.[10]

Drug interactions: Consult appropriate resources for dosing recommendations before combining any drug with indomethacin.

Renally-based interactions: Digoxin is dependent on renal function for elimination; hence, the dose may need to be reduced when used with indomethacin. Additional monitoring with ECGs or serum digoxin concentrations may be needed to detect digoxin toxicity.[10,34,42] Concurrent aminoglycoside and indomethacin (standard course was given every 8 hours) produced elevation in peak and trough aminoglycoside serum concentrations.[10,43] Concomitant therapy with indomethacin and furosemide may dampen natriuresis resulting in greater urinary output, greater sodium and chloride excretion, and higher GFR compared to indomethacin alone; this suggests that furosemide may offer some renal protection.[10]

Other: Indomethacin is a minor substrate of CYP2C9 and 2C19, and it is a strong inhibitor of CYP 2C9.[18] It is also bound to albumin and could displace bilirubin from albumin-binding sites.[44]

Infliximab

Brand names

Remicade

Medication error potential

Look-alike, sound-alike drug names.

ISMP and USP report that rituximab has been confused with infliximab.[1,2] USP reports that this error caused patient harm.[2]

Contraindications and warnings

U.S. boxed warnings

Risk of serious infections: Patients receiving infliximab are at risk for developing serious infections. Those with active infections should not begin treatment. Those who develop infection while on treatment should be monitored closely.[3,4]

Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test. If the skin test is positive, treatment of tuberculosis should be started prior to beginning treatment with infliximab.[3,4] (See Comments section.)

Hepatosplenic T-cell lymphomas: These have been reported in adolescents and young *adults* receiving infliximab. These cases occurred in patients with Crohn disease or ulcerative colitis who were receiving concomitant azathioprine or 6-mercaptopurine.[3,4]

FDA alert: On August 4, 2009, the FDA announced that it is requiring those who manufacture tumor necrosis factor (TNF) blockers to update the boxed warning to include an increased risk of lymphoma and other cancers in children and adolescents treated with TNF blockers.[5]

Contraindications: Patients who have had a previous severe hypersensitivity reaction to infliximab should not receive any additional doses.[3]

Patients with severe heart failure should not receive infliximab doses >5 mg/kg.[3]

Other warnings: Anaphylactic type reactions have been reported.[3] Appropriate medical care should be available in the event this occurs.

Hepatotoxicity has been reported, sometimes requiring transplantation. Infliximab should be discontinued in patients with jaundice and/or marked liver enzyme elevations.[3]

Infusion-related cautions

Flushing, chest pain, and shortness of breath have occurred during infusion in up to 38.6% of pediatric patients.[6–9] Acetaminophen, antihistamines, corticosteroids, and epinephrine, or by slowing the rate of infusion aids in symptom management.[3,4,8] The infusion should be stopped if this regimen symptoms do not improve or if epinephrine is required. Infusion reactions can occur with the first or any subsequent dose[6] but are most likely to occur after the second or third infusion.[4,6] A history of an infusion reaction is not predictive of future infusion-related reactions.

A delayed infusion reaction may be experienced 3–5 days after treatment. The physician should be notified if this occurs. Longer intervals between treatments (more than a year) increase the risk of delayed infusion reactions.[3,4]

Dosage

Premedication with antihistamines, acetaminophen and/or corticosteroids may be used to prevent or manage infusion-related reactions.

Crohn disease: Usual doses are 5 mg/kg repeated PRN.[10–19] Regimens include 5 mg/kg q 8 wk for a year if showing a favorable response,[15] 5 mg/kg at 0, 2, and 6 weeks followed by 5 mg/kg q 8 wk,[15–18] and 5 mg/kg administered on days 0, 15, and 45.[19] Doses of 1 mg/kg are less effective.[20]

Ulcerative colitis: 5 mg/kg[21–24] initially followed by 5–10 mg/kg in 2 weeks[22] or 5 mg/kg as induction therapy at 0, 2, and 6 weeks with maintenance treatment q 6–8 wk.[12,23,24]

Dosage *(cont.)*	**Refractory juvenile idiopathic arthritis (JIA):** 3–4 mg/kg initially or at weeks 0, 2, and 6 weeks followed by up to 10 mg/kg q 4–8 wk.[25,26] One study in 122 children who were receiving methotrexate found that infusion reactions were greater in the group receiving 3 mg/kg than those receiving 6 mg/kg.[27] **JIA uveitis:** 5–10 mg/kg at weeks 0, 2, and 4 followed by infusions q 6–8 wk with a more rapid infusion rate based on tolerance (stable vital signs).[28] In a case series of pediatric uveitis patients with or without associated JIA, all patients responded to infliximab at 5–10 mg/kg at 2–8 week intervals.[29] (See Comments section.) **Refractory Kawasaki syndrome:** Limited data suggests that a single infusion of 5–10 mg/kg may be beneficial in patients who have not responded to 2 doses of IV immunoglobulin and high-dose daily aspirin therapy.[30]
Dosage adjustment in organ dysfunction	Information not available.
Maximum dosage	Doses up to 20 mg/kg have been used in *adults,*[3] and one case series reported successful treatment of a 15-year-old patient receiving a dose of 18 mg/kg.[29]
Additives	None.[3,4]
Suitable diluents	SW to reconstitute, NS to dilute.[3,4]
Maximum concentration	4 mg/mL.[3,4]
Preparation and delivery	**Preparation:** Reconstitute a 100-mg vial by adding 10 mL SW via a 21-gauge or small needle with the stream directed to the glass wall of the vial. Gently rotate the vial to dissolve. Do not shake. The reconstituted vial should be allowed to sit for 5 minutes prior to dilution.[3,4] After the total dose (which may include multiple vials) has been reconstituted, withdraw an equivalent dose volume of NS from a 250-mL bag or bottle. Slowly add the total volume of reconstituted infliximab to the 250-mL bag or bottle. Gently mix.[3,4] **Stability:** The vial contains no preservatives and once reconstituted the infusion must begin within 3 hours.[3,4] **Delivery:** Administer the infusion using an in-line, low-protein-binding filter with a pore diameter ≤1.2 microns.[3,4] The infliximab infusion should be administered over a period not less than 2 hours.[4]
IV push	Not indicated.[3,4]
Intermittent infusion	The infusion rate was increased after 15 minutes from 15 mL/hr to 30 mL/hr for 15 minutes to 60 mL/hr for 30 minutes to 90 mL/hr to complete the infusion[4,15] or was increased q 15 min from 10 mL/hr to 20 mL/hr to 40 mL/hr to 80 mL/hr to a maximum of 125 mL/hr based on the stability of vital signs.[4,6] The infusion should be administered over ≥2 hours.[3,4]
Continuous infusion	Not indicated.

Infliximab

Other routes of administration	Not indicated.

Comments

JIA, juvenile rheumatoid arthritis, and juvenile chronic arthritis may be used interchangeably.

A negative skin test for tuberculosis does not rule out the possibility of disease since patients with immune diseases may exhibit cutaneous anergy.[31]

Infusion-related reactions are believed to be caused by the production of antibodies to infliximab. The concomitant administration of immunomodulating medications (or use within the preceding 4 months) is believed to be protective.[3]

Infliximab was a more effective therapy for JIA uveitis than etanercept.[32,33]

Drug interactions: Patients receiving anakinra and abatacept should not receive infliximab due to a possible increased risk for infection.[3]

Live-virus vaccines (measles, mumps, rubella; varicella; rotavirus) should be avoided during treatment.[3,4] It is recommended that all pediatric patients should be brought up to date on vaccinations prior to beginning therapy with infliximab.[4]

Infliximab can cause reactivation of hepatitis B virus (HBV). Patients should be tested for HBV prior to therapy, and if reactivation occurs, infliximab should be discontinued.[3]

Insulin

Brand names	HumuLIN R, NovoLIN R, HumuLIN R (concentrated U-500)
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP reports that HumuLIN R has been confused with HumaLOG and NovoLIN.[2] USP reports that HumuLIN R has been confused with HumuLIN 70/30, NovoLIN 70/30, NovoLIN R, and NovoLOG. Patient harm resulted when HumuLIN R was confused with HumaLOG.[3] USP reports that NovoLIN R has been confused with HumuLIN R. Patient harm resulted when NovoLIN R was confused with NovoLIN 70/30, NovoLIN GE NPH, and NovoLOG.[3]
Contraindications and warnings	**FDA alert:** On March 19, 2009, the FDA reminded healthcare providers and patients that insulin pens must not be shared due to the potential of transmission of viruses (including HIV and hepatitis C) and other blood borne pathogens. **Contraindications:** Hypersensitivity to regular insulin or any of its components; hypoglycemia.[4,5] **Warnings:** Hypoglycemia is the most common adverse effect.[4,5] Serum glucose concentrations must be monitored closely to detect hypoglycemia early. Accurate choice of product is critical since many different types of insulin preparations are available. Availability and use of concentrated insulin should be restricted.
Infusion-related cautions	Regular insulin products can be infused intravenously.[4–6]
Dosage	**Hyperglycemic crises in diabetes (diabetic ketoacidosis [DKA] and hyperosmolar hyperglycemic state [HHS]):** Biochemical evidence of DKA includes $HCO_3 < 15$ mmol/L, pH < 7.25 and an increased blood glucose (BG). Baseline electrolytes must be obtained and rehydration with NS should be done prior to beginning insulin as BG concentrations will begin to decrease with rehydration. Institutional protocols for fluid and electrolyte replacement, monitoring and use of insulin should be followed.[7] Initially, 0.05–0.1 unit/kg/hr.[7–13] A loading dose is no longer recommended.[7] Blood glucose should be measured hourly to ensure that the decrease in BG is 50–90 mg/dL/hr.[7] Too rapid a decrease in BG may cause cerebral edema and may require the addition of a glucose infusion even before glucose is <300 mg/dL. If the biochemical parameters of DKA do not improve, the insulin infusion may be increased. SC dosing can be started when the $HCO_3 \geq 18$ mmol/L, pH > 7.3 and BG < 200 mg/dL.[7] **Hyperkalemia (after or with $NaHCO_3$ and calcium gluconate):** 0.05–0.1 unit/kg/hr infused with 400 mg dextrose/kg or 1 unit insulin/4 g dextrose.[12,14–16] A systematic review included two unblinded studies in preterm neonates.[17] One of these reported that 20 infants who received 1 unit insulin/10–15 g dextrose had shorter duration of hyperkalemia and fewer episodes of intraventricular hemorrhage than those (n = 20) receiving sodium polystyrene sulfonate. However, authors of the review concluded that no firm practice recommendations could be made for preterm neonates. **Hyperglycemia:** The consensus target BG range for most critically ill patients is 140–180 mg/dL. The best method to attain this BG and avoid hypoglycemia is unknown; institutional protocols including frequent monitoring and safeguards against hypoglycemia are encouraged.[18]

Dosage *(cont.)*	**Critically ill children:** Initial infusion rates of 0.01–0.2 unit/kg/hr[19–26] titrated to achieve euglycemia have demonstrated (in retrospective and randomized controlled trials) reductions in morbidity (reduced infections and inflammatory markers in critically ill patients, and enhanced insulin sensitivity with reduced resting energy expenditure in severely burned children).[20,21,26] Rates of hypoglycemia were as high as 30%.[21,25,26] Some protocols have successfully reduced hypoglycemia rates.[19] **Glucose intolerance in premature low birth weight (LBW) infants:** A 2008 multicenter trial compared early insulin treatment in 195 LBW infants (0.05 unit/kg/hr with D20W to maintain euglycemia) within 24 hours of age to conventional therapy (sliding scale and infusion starting at 0.05 unit/kg/hr) in 194 infants (with dextrose titrated to avoid hyperglycemia [BG >180 mg/dL] and hypoglycemia [BG <47 mg/dL]). The trial was ended early because of increased mortality at 28 days of life in the early group (11.9% versus 5.7%; odds ratio 0.45, confidence interval 0.21–0.96).[27] A 2012 randomized controlled trial of 88 premature infants who received insulin to achieve tight glycemic control (0.05 unit/kg/hr titrated to achieve BG 70–108 mg/dL compared to standard glycemic control) found no improvements in mortality or increased hypoglycemia (<47 mg/dL; 58% in tight control group), but found a decrease in linear growth. Authors concluded that insulin may not be safe or effective for neonatal glucose intolerance.[28] Earlier studies evaluated 0.03–0.08 unit/kg/hr with the dose titrated to desired BG concentration.[29–34] (See the following sections: Maximum Dosage, Preparation and Delivery, and Comments.)
Dosage adjustment in organ dysfunction	If CrCl 10–50 mL/min (*adult* recommendation), give 75% of the normal dose.[35] If CrCl <10 mL/min (*adult* recommendation), give 50% of normal dose.[35] Use cautiously in patients with hepatic impairment.[4,5,36]
Maximum dosage	Up to 4.2 units/kg/hr were required occasionally in hyperglycemic very low birth weight neonates (<1000 g) during first 2 weeks of life.[33,34] It has been speculated that the increased requirement in these infants was due to insulin resistance, inappropriate insulin secretion, or decreased sensitivity of the liver to insulin effects.[32,37] In DKA, some endocrinologists do not use more than 3 units/hr in children.[8]
Additives	100 units contain 7–15 mcg Zinc.[4,5] Novolin R contains glycerol and metacresol.[4] Humulin R contains glycerin and metacresol.[5]
Suitable diluents	**Humulin R:** D5W, NS.[5,6] **Novolin R:** NS, D5W, or D10W with 40 mmol/L potassium chloride.[4]
Maximum concentration	0.1–1 unit/mL depending on the dose to be delivered and limitations of infusion devices.[4,5] 100 units/mL (commercially available) for IM or SC dosing.[4,5]
Preparation and delivery	Insulin binds to glass bottles, plastic IV bags, syringes, and tubing and results in decreased delivery of insulin. IV tubing may be primed with an insulin solution to saturate insulin-binding sites and prevent further absorption.[6,31,38,39] Alternatively, human serum albumin occupies binding sites on glass[40] and plastic and has been added to insulin-containing solutions[7,29,32] to increase insulin delivery. **Compatibility:** See Appendix D for PN compatibility information.

Insulin

IV push	A loading dose has been used in DKA and HHS[8] but is no longer recommended.[7]
Intermittent infusion	Not indicated.
Continuous infusion	Commonly used. (See Dosage section.)
Other routes of administration	SC; IM administration has been reported[8] but is not recommended by manufacturers.[4,5] In DKA and HHS, these routes of administration may require hourly dosing of insulin. IM and SC dosing should not be used in patients with hypovolemic shock, hyperosmolar hyperglycemia, or hyperkalemia. A 5-year-old with DKA and dehydration received insulin via IO infusion.[41]
Comments	**Blood glucose measurements:** 120 mg/dL = 6.7 mmol/L. In LBW infants, a 12- to 14-hour delay in response was noted when IV tubing was not primed with insulin.[31] Whether this was due to lack of priming or insulin resistance was not evaluated. **Monitoring:** It is essential that BG concentrations be measured regularly during insulin therapy to avoid hypoglycemia. Bedside measurements should be periodically compared to plasma samples performed in the laboratory to insure their accuracy. **DKA**[7]**:** Electrolytes, magnesium, phosphorous, and blood gas must be measured every 2–4 hours or more frequently if clinically indicated. BUN, SCr, and hematocrit should be measured every 6–8 hours. Intake and output should be measured hourly along with neurological assessments and vital signs. **Hyperkalemia:** Serum potassium concentrations and BG. Treatment should be discontinued when potassium concentrations are normalized.

Interferon Alfa-2b

Brand names	Intron A for Injection
Medication error potential	Look-alike, sound-alike drug names. USP reports that interferon alfa-2a has been confused with interferon alfa-2b.[1]
Contraindications and warnings	**U.S. boxed warning:** Alpha interferons cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely, and periodic clinical and laboratory valuations should be performed. Treatment should be stopped in patients with persistently severe or worsening signs or symptoms of these conditions. In many cases, but not all, these disorders resolve after therapy is discontinued.[2] **Contraindications:** Hypersensitivity to interferon alfa-2b or product components, autoimmune hepatitis, and decompensated liver disease.[2] **Warnings:** Should be used with caution in patients with a history of pulmonary disease, diabetes mellitus with a history of diabetic ketoacidosis, and in patients with coagulation disorders or severe myelosuppression.[2]
Infusion-related cautions	The solution vials for injection and the multidose pens for injection are not indicated for IV use.[2] Injection site reactions occur in 5% of pediatric patients with chronic hepatitis B.[2]
Dosage	**Chronic hepatitis B with compensated liver disease:** 3 million units/m^2 SC or IM 3 times/week for 1 week, then increased to 6 million units/m^2 SC 3 times/week for 16–24 weeks.[2] Children from 3–15 years of age have been treated with 3–10 million units/m^2 SC or IM[3–9] 3 times/week for up to 1 year, alone or in combination with lamivudine.[10,11] Larger doses are associated with higher rates of viral clearance.[4] (See Comments section.) **Chronic hepatitis C:** Children ≥2 years of age have received 3–5 million units/m^2 SC 3 times/week[12–15] or 0.1 million unit/kg/day for 2 weeks then 3 times/week for 26 weeks.[16] (See Comments section.) **Melanoma:** In a small tolerability study, 15 children from 1.5–17 years old received induction therapy with 20 million units/m^2 IV 5 times/week for 4 weeks. This was followed by 10 million units/m^2 SC 3 times/week for 48 weeks.[17] **Hemangiomas or Kasabach-Merritt syndrome:** 100,000–6 million units/m^2/day SC for ≥9 weeks.[18–21] One group treated 39 children from 1.5–158 months of age with 3 million units/m^2/day SC for 6 months.[21] Treatment continued for another 6 months, and in those who responded the interval was changed to 3 times/week; however, in those without hemangioma regression, the dose was increased to 6 million units/m^2/day SC.[21] In Kasabach-Merritt syndrome (an aggressive vascular tumor), six of eight children responded to 3 million units/day that was given for up to 12 months.[22] **Relapsed T-cell acute lymphoblastic leukemia (ALL) or non-Hodgkin lymphoma (NHL):** Twenty children from 3–18 years of age were given 30 million units/m^2/day to 3 times/week IV or SC; two of these developed congestive heart failure.[23] Doses from 3–50 million units/m^2 for 10 doses in 2 weeks were used in a limited number of pediatric patients with ALL, NHL, and Philadelphia chromosome–positive chronic myelogenous leukemia.[24]
Dosage adjustment in organ dysfunction	Recommendations for dosage decreases are according to hematologic indices, liver, and renal function. In addition, recommended dosage changes vary according to disease being treated. (See Comments section.) Interferon alfa-2b may be used in combination with ribavirin for the treatment of hepatitis C and hepatitis B. This combination should not be used in patients with CrCl <50 mL/min.

Dosage adjustment in organ dysfunction *(cont.)*

Chronic hepatitis B

Dose	WBC	Granulocytes	Platelets
Decrease 50%	$<1.5 \times 10^9$/L	$<0.75 \times 10^9$/L	$<50 \times 10^9$/L
Discontinue	$<1 \times 10^9$/L	$<0.5 \times 10^9$/L	$<25 \times 10^9$/L

Malignant melanoma (during induction or maintenance therapy)[2]

Withhold doses: Granulocytes >250 mm^3 but <500 mm^3; ALT/AST >5 to ≤10 × upper limit of normal (restart at 50% of initial dose once normal).

Permanently discontinue: Granulocytes <250 mm^3 or ALT/AST >10 × upper limit of normal.

Follicular lymphoma[2]

Withhold doses: Neutrophil count <1000/mm^3 or platelet count <50,000/mm^3.

Decrease dose 50%: Neutrophil count >1000/mm^3 but <1500/mm^3.

Permanently discontinue: SCr >2 mg/dL or AST >5 × upper limit of normal.

Maximum dosage

Children with chronic hepatitis B: 10 million units 3 times/week.

***Adults* with chronic hepatitis B:** 35 million units IM or SC/week for 16 weeks.[1]

Additives

When the lyophilized powder is reconstituted with the provided diluent (SW), each mL contains 20 mg glycine, 2.3 mg sodium phosphate dibasic, 0.55 mg sodium phosphate monobasic, and 1 mg albumin (human).[1]

Each mL of the solution vials for injection (given IM, SC, intralesional) and the multidose pens for injection (given SC) contain 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg *m*-cresol.[2]

Suitable diluents

NS.

Maximum concentration

≥10 million units/100 mL for IV infusion.[2]

Concentrations for SC and IM use range from 6–50 million units/mL depending on the product and indication.[2]

Preparation and delivery

The lyophilized powder is reconstituted with the provided diluent (SW).[2] After the diluent is added, swirl the vial gently to dissolve the powder, do not shake. The reconstituted powder is suitable for IM or SC administration. For IV infusion, the reconstituted dose should be withdrawn and added to 100 mL of NS. The final concentration for IV infusion should be ≥10 million units/100 mL. This contains no preservative and should be discarded after the first dose is withdrawn.

Multidose vials (IM, SC) and pens (SC) are available in a variety of concentrations that are ready to use.[2]

Stability

Store powder and solution for injection under refrigeration at 2°C to 8°C; do not freeze.

Powder for injection: Following reconstitution may be stored in refrigerator up to 24 hours.

Prefilled pens: After first use, discard unused portion after 4 weeks.

Interferon Alfa-2b

IV push	Not indicated.
Intermittent infusion	Over 20 minutes.[2]
Continuous infusion	Not indicated.
Other routes of administration	IM, SC.[2]
Comments	**Adverse effects:** A flu-like syndrome of fever, fatigue, malaise, myalgia, chills, headache, arthralgia, and rigors occurs frequently.[2,3,7,18,25] Severity of this increases with higher dosages.[2,3,7,18] Fevers peak within 6 hours and may persist for up to 12 hours. Pretreatment with antipyretics (e.g., APAP or NSAIDs) may be beneficial. Dosing at night may decrease the flu-like adverse effects.[2] Children may exhibit significant changes in body weight, linear growth, BMI, and body composition.[27] Ischemic retinopathy and uveitis have been reported in children treated for hepatitis C with or without ribavirin.[28] Interferon alfa-2b used in combination with ribavirin for the treatment of hepatitis C and hepatitis B resulted in hemolytic anemia in 10% of patients. **Monitoring:** CBC with differential and platelet count pretreatment and routinely during therapy, blood glucose, liver function tests, renal function tests, thyroid-stimulating hormone levels, triglyceride levels, chest x-ray, and neuropsychiatric monitoring.[2] **Drug interactions:** Interferon decreases theophylline clearance.[2,26] Theophylline serum concentrations should be monitored during treatment. Interferon alfa may enhance the adverse/toxic effect of clozapine. Specifically, the risk of agranulocytosis may be increased.

Irinotecan HCl

Brand names	Camptosar, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that irinotecan has been confused with topotecan; no patient harm resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** Irinotecan must be administered under the supervision of physician experienced with chemotherapeutic agents. Irinotecan can induce both late and early forms of diarrhea and severe myelosuppression can occur.[3] (See Significant Adverse Effects in the Comments section.) **Contraindications:** Irinotecan is contraindicated in patients with known hypersensitivity to the drug or any of its components.[3] **Other warnings:** May cause severe diarrhea, neutropenia, hypersensitivity, colitis/ileus, renal impairment, interstitial pulmonary disease symptoms, severe emesis, and risk of thromboembolism.[3,4] (See Significant Adverse Effects in the Comments section.)
Infusion-related cautions	A higher incidence of cholinergic side effects has been reported with shorter infusion times.[5] Extravasation should be avoided. If extravasation occurs, flush site with sterile water and apply ice.[3]
Dosage	Consult institutional protocol for complete dosing information. Irinotecan is used as a component of combination therapy or as a single agent to treat multiple pediatric tumors, including neuroblastoma, hepatocellular tumors, Wilms tumor, Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, and CNS tumors, including medulloblastoma, ependymomas, brain stem gliomas, and astrocytomas.[4] **Refractory solid tumors (low-dose, protracted schedule):** 20 mg/m^2/day for 5 days for 2 consecutive weeks repeated q 21 days.[3–6] **Refractory solid tumors or CNS tumors:** 50 mg/m^2/day for 5 days repeated q 21 days.[4,7–9] **Heavily pretreated refractory solid tumors or CNS tumors:** 125 mg/m^2/dose once weekly for 4 weeks, repeated q 6 wk.[4,10] **Less heavily pretreated refractory solid tumors or CNS tumors:** 160 mg/m^2/dose once weekly for 4 weeks, repeated q 6 wk.[4,10]
Dosage adjustment in organ dysfunction	No information to guide administration of irinotecan in patients with hepatic (i.e., serum bilirubin >2 mg/dL) or renal dysfunction.[3] Some studies suggest that patients with moderate hepatic dysfunction (i.e., serum bilirubin of 1–2 mg/dL) and a prior history of abdominal or pelvic radiation may be at increased risk of developing neutropenia.[11] Some clinicians reduce dose in this scenario.
Maximum dosage	Not established. In clinical trials, single dosages up to 345–750 mg/m^2 have been administered to *adult* cancer patients.[3] No antidotes for overdoses are known. Patients should receive supportive care to prevent neutropenia and diarrhea.
Additives	None.

Irinotecan HCl

Suitable diluents	D5W, NS.[3,12]
Maximum concentration	2.8 mg/mL.[3,12]
Preparation and delivery	**Preparation:** Irinotecan must be diluted prior to infusion. Most clinical trials have used 250–500 mL of D5W as a diluent, as the relatively acidic pH of irinotecan favors dilution with D5W over NS.[3,11,12] **Stability:** Do not refrigerate solutions mixed in NS since visible particulates may develop.[4]
IV push	Not recommended.
Intermittent infusion	Dilute with suitable diluent to a final concentration of 0.12–2.8 mg/mL and infuse over 60–90 minutes.[3]
Continuous infusion	Hepatic arterial continuous infusions have been explored in *adult* colorectal cancer patients with metastases to the liver.[13]
Other routes of administration	No information available to support administration by other routes.

Comments

Significant adverse effects: Irinotecan is associated with both acute (within first several hours) and delayed (24 hours after drug administration) diarrhea, both of which can be dose-limiting.[3] Patients should be premedicated with 0.01 mg/kg of IV atropine (maximum dose: 0.4 mg) to prevent acute diarrhea and should receive a prescription for loperamide to prevent delayed diarrhea. Acute diarrhea is usually transient and patients may develop cholinergic symptoms such as rhinitis, miosis, flushing, or lacrimation. However, delayed diarrhea can have life-threatening consequences, such as dehydration, electrolyte disturbances, fever, or severe neutropenia.[3] If patients develop late diarrhea, loperamide should be administered every 3 hours while the patient is awake and every 4 hours while the patient is asleep for up to 24 hours after complete resolution of loose stools. Please note that this loperamide regimen differs from what is listed on the package insert for OTC cases of diarrhea. The table below lists the suggested doses based on weight of the child.[4]

Dose of Loperamide Based on Weight of Patient

Weight (kg)	Immediate Dose	Daytime Dose (q 3 hr)*	Nighttime Dose (q 4 hr)
8–10	1 mg	0.5 mg	0.75 mg
10.1–20	1 mg	1 mg	1 mg
20.1–30	2 mg	1 mg	2 mg
30.1–43	2 mg	1 mg q 2 hr	2 mg
>43	4 mg	2 mg q 2 hr	4 mg

*Unless noted.

Cephalosporins, such as cefixime and cefpodoxime, have been shown to decrease the incidence of diarrhea and allow for dose escalations of up to 50% in children receiving IV irinotecan.[14–16]

Irinotecan HCl

Comments *(cont.)*

Patients that develop severe neutropenia and/or diarrhea while on normal dosages of irinotecan may need pharmacogenetic testing to evaluate if they are homozygous for the UGT1A1 allele that has been associated with increased irinotecan side effects.[3] Homozygous patients may require a dosage reduction.

Patients should have a baseline absolute neutrophil count >1500 cells/mm^3 and a platelet count >100,000 cells/mm^3 before drug administration.[3] The manufacturer has outlined dosage reductions for diarrhea, neutropenia, and neutropenic fever in the labeling.[3]

Irinotecan is associated with a moderate (30% to 90%) risk of emesis.[17] Patients should receive antiemetic therapy to prevent acute and delayed nausea and vomiting. The recommended therapy is a 5HT3 receptor antagonist in combination with dexamethasone on every day chemotherapy is administered.[17,18] These agents may be continued for up to 4 days after chemotherapy administration for the prevention of delayed nausea and vomiting. Breakthrough medications should also be offered, such as a phenothiazine (e.g., prochlorperazine), a butyrophenone (e.g., droperidol), a substituted benzamide (e.g., metoclopramide), or a benzodiazepine (e.g., lorazepam).

Monitoring: Patients should be monitored for signs of diarrhea and dehydration, electrolytes, BUN and SCr, CBC and platelet counts, and liver enzymes. Infusion site should also be monitored for signs of inflammation.[3,4]

Drug interactions: Irinotecan is a major substrate for CYP2B6 and CYP3A4 and thus concomitant administration with other medications that interact with similar isoenzymes should be approached with caution.[3,4] Consult appropriate resources for dosing recommendations before combining any drug with irinotecan.

Iron Dextran

Brand names

DexFerrum, INFeD

Medication error potential

Iron dextran products are available in two formulations: a high-molecular-weight (DexFerrum) and a low-molecular-weight (INFeD) formulation. Because these are not clinically interchangeable, care should be taken to verify the product and dose. This is especially true when substituting one form of iron for another as significant dosing errors can occur.

Look-alike, sound-alike drug names. DexFerrum has been confused with Desferal; however, no patient harm resulted.[1]

Contraindications and warnings

U.S. boxed warning: Parenteral iron is associated with anaphylactic-type reactions, which have caused death.[2] Use particular caution in patients with multiple drug allergies.[2] During infusion, patients should be monitored for signs and symptoms of anaphylactic reaction.[2] Administer only when resuscitation equipment and personnel trained to detect and treat anaphylactic reactions are readily available.[2] (See Comments section.)

Infusion-related cautions

Acute reactions include hypotension, bronchospasm, pharyngeal/angioedema, urticaria, and pruritus.[3–6] Premedication does not appear to decrease the incidence of acute reactions. (See Comments section.)

Dosage

Parenteral iron therapy should be reserved for patients with iron deficiency who are unable to take iron orally.[2]

Test dose: A one-time test dose should be administered prior to initiating therapy.

Weight	Test Dose
<10 kg	10 mg
10–20 kg	15 mg
>20 kg	25 mg

Others have recommended the use of the standard *adult* test dose of 25 mg.[8–11] Guidelines for the use of parenteral iron in children with renal disease recommend a weight-adjusted test regimen.[7] Test doses should be administered slowly over ≤50 mg/min followed by the administration of the remainder of the initial dose 1 hour after the test dosing is complete.[2,12,13] Anaphylactic reactions occur with the first few minutes of infusion; therefore, immediate access to emergency medications (i.e., epinephrine) and trained personnel should be available.[2,12] (See Comments section.)

Some practitioners suggest that the daily dose be added to PN solutions, and heart rate, blood pressure, respiration, and temperature can be monitored every 15 minutes for the first hour of the initial dose.[9] (See Infusion-Related Cautions section.)

Anemia of prematurity: In conjunction with erythropoietin therapy, 0.2–1 mg/kg/day.[14,15] Alternatively, 5 mg/kg/week has been added to PN solutions or infused over 4–6 hours.[16] Doses up to 10 mg/kg/week of iron dextran have been used to maintain serum ferritin levels.[16]

In conjunction with erythropoietin, alternative forms of parenteral iron (iron sucrose) have used doses of 2 mg/kg/day and up to 20 mg/kg/week.[17,18]

Iron-deficiency anemia: The deficiency (mL of iron dextran) can be calculated based on hemoglobin (Hb)[2]:

5–15 kg

$$\text{Total iron dose (mL)}^{*} = 0.0442\ (\text{Desired Hb}^{\dagger} - \text{Observed Hb}) \times \text{wt (kg)} + (0.26 \times \text{wt [kg]})$$

*50 mg/mL, undiluted product.

†Desired Hb for children is usually 12 g/dL.

>15 kg

The same equation is used. However, the individual's lean body mass (LBM) in kg is substituted for weight in obese individuals. The LBM can be calculated in those >5 feet tall as follows:

LBM (males) = 50 kg + 2.3 kg for each inch over 5 feet.

LBM (females) = 45.5 kg + 2.3 kg for each inch over 5 feet.

≤100 mg (up to 2 mL) may be administered daily until the calculated amount to correct the deficit is achieved.[2]

Correction secondary to blood loss[2]: The deficit can be calculated based on hematocrit (Hct).[19]

Total iron dose (mL)* = 0.02 × Blood loss (mL) × Hct (as decimal fraction)

*50 mg/mL, undiluted product.

Long-term PN: Maintenance dose of 0.11–0.15 mg/kg/day[20–22] or monthly infusion of estimated requirements. (See Continuous Infusion section.)

Iron deficiency in hemodialysis (HD) patients with chronic renal failure: *The National Kidney Foundation Guidelines for Chronic Anemia* recommend weight-adjusted dosing of iron dextran in children[12,23]:

	Patient Weight		
	<10 kg	**10–20 kg**	**>20 kg**
Each dose or dialysis × 10 doses	0.5 mL (25 mg)	1 mL (50 mg)	2 mL (100 mg)

Alternatively, 2–4 mg/kg (≤100 mg) 3 times per week for 10 doses during erythropoietin therapy.[11,24]

Iron deficiency in peritoneal dialysis patients with chronic renal failure: *The National Kidney Foundation Guidelines for Chronic Anemia* recommend weight-adjusted dosing of iron dextran in children.[12] This dose can be repeated to maintain adequate iron stores.

	Patient Weight		
	<10 kg	**10–20 kg**	**>20 kg**
Iron dose	125 mg	250 mg	500 mg
Volume of saline for infusion	75 mL	125 mL	250 mL

Dosage adjustment in organ dysfunction

No information available; however, considering the distribution characteristics of iron, there should be no dose adjustment necessary relative to liver or kidney function. However, guidelines for the use of parenteral iron in children with renal disease recommend an adjustment in the dose of the test regimen.[7] We also need to refer the reader (see Dosage; Iron deficiency in peritoneal dialysis patients with chronic renal failure.)

Maximum dosage

In most cases, daily doses should not exceed the following weight-based doses.[2] If <5 kg, give 25 mg; if ≥5 kg but ≤10 kg, give 50 mg; and if >10 kg, give 100 mg.

Additives

None reported.

Suitable diluents

The manufacturer does not recommend since the product was originally developed for IM use. However, dilution with NS is preferred for IV administration.[8,11,13] Although dextrose solutions may be used, it may increase the incidence of phlebitis.[13]

Iron Dextran

Maximum concentration	50 mg/mL.[2,12]
Preparation and delivery	**Preparation:** Iron dextran is a dark brown, slightly viscous liquid complex of ferric hydroxide and dextran in NS providing 50 mg of elemental iron per milliliter. **Compatibility:** Although not recommended by the manufacturer, iron dextran has been administered in PN formulations. Results of studies evaluating iron dextran stability and compatibility in PN solutions are inconsistent.[25,26] To ensure compatibility, the PN solution should contain at least 2% amino acids (10 mg iron dextran/L was visually compatible in neonatal PN solutions containing at least 2% amino acids).[27] (For additional PN compatibility information, see Appendix D.)
IV push	Test dose should be infused over at least 30 seconds (INFeD) or 5 minutes (Dexferrum). May be administered undiluted (50 mg/mL) at a rate <50 mg/min.[2,13] (See Infusion-Related Cautions section.)
Intermittent infusion	Dilute in NS and infuse over 4–6 hours.[2,13]
Continuous infusion	The iron deficit can be replaced over several days by adding iron to PN solutions in daily amounts not exceeding the maximum daily recommendations.[20–22,28] (See Maximum Dosage section.)
Other routes of administration	Although the IV route is preferred, iron dextran has been administered IM using Z-track technique into upper quadrant of buttock.[2,13] May be associated with pain, staining of skin, tissue necrosis or abscess, and sarcoma development at the injection site.[29] Staining of the skin can be minimized by using a separate needle to withdraw the drug from the container and by displacing the skin laterally prior to injection.[13]
Comments	**Significant adverse drug reactions:** Patients with drug allergies may be at increased risk of anaphylactic-type reactions.[2] Although a test dose should be administered prior to the first therapeutic dose,[2] deaths have occurred following a test dose, as well as during administration of therapeutic doses after a test dose was tolerated.[2] In fact, successful receipt of test doses or prior therapeutic doses does not ensure safety since most patients who develop severe reactions have received prior doses without incident.[19] Acute and delayed hypersensitivity reactions have been reported at a higher rate with iron dextran than other parenteral iron products in large *adult* studies.[3–6] One study reported a higher rate of hypersensitivity reactions with the higher molecular weight dextran (Dexferrum) than the lower molecular weight (InFeD) product.[4] A hypersensitivity reaction to one parenteral iron product does not predict a similar response to a different product. Delayed reactions such as arthralgias, myalgias, headache, fever, and lymphadenopathy may appear 24–48 hours after infusion. **Monitoring:** Serum ferritin monitoring is recommended to prevent potential iron overload.[2,12,19] A 2007 update to the KDOQI guidelines for the treatment of anemia in chronic kidney disease addressed the target hemoglobin range. The recommendations specified a target hemoglobin concentration of 11–12 g/dL for pediatric dialysis and nondialysis patients with chronic kidney disease receiving erythropoietin-stimulating agents.[30]

Isoproterenol HCl

Brand names	Isuprel, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that isoproterenol has been confused with isosorbide mononitrate. Isuprel has been confused with Inderal.[2]
Contraindications and warnings	**Contraindications:** Use in patients with tachyarrhythmias, tachycardia, or heart block due to digoxin toxicity, ventricular arrhythmias requiring inotropes, and angina pectoris.[3] **Warnings:** Not recommended as the initial treatment of cardiogenic shock following myocardial infarction.[3]
Infusion-related cautions	Cardiac dysrhythmias[3,4] and abnormal ECG and enzymatic findings suggestive of myocardial dysfunction have been reported in pediatric patients.[5,6] Although rare in pediatric patients, myocardial ischemia may occur.[3,5–8] Two adolescents with severe asthma who were treated with isoproterenol had myocardial necrosis at autopsy.[7,8]
Dosage	Doses in neonates and children range from 0.03–2 mcg/kg/min, usually starting at a lower dose and titrated to desired response.[4,9–12] In *adults*, initial IV bolus doses range from 0.02–0.06 mg with subsequent doses ranging from 0.01–0.2 mg; continuous infusion starts at 5 mcg/min and is titrated to desired response PRN[3] to 20 mcg/min.[13] Newer therapies have largely replaced its use in the treatment of shock and pulmonary hypertension.[9,14,15] **Asthma:** Not recommended due to risks of myocardial toxicity.[16] **Cardiac arrhythmias and CPR:** No longer considered a drug of choice. The *2010 American Heart Association Pediatric Advanced Life Support Guidelines* did not include isoproterenol for use in bradycardia (a change from the previous version).[17,18] Recommended dosing for this indication was an initial rate of 0.1 mcg/kg/min with a usual range of 0.1–1 mcg/kg/min.[3] **Head-up tilt testing for syncope:** 1–3 mcg/min IV for 20 minutes (adolescents)[19] or 0.02–0.08 mcg/kg IV in escalating doses q 2 min for ≤20 minutes, targeting a heart rate of 150 beats/min.[20]
Dosage adjustment in organ dysfunction	Doses in the lower ranges for a given indication are recommended in patients with cardiac, hepatic, or renal dysfunction.[3]
Maximum dosage	Critically ill children from 2 days to 14 years of age received doses ≤5.5 mcg/kg/min (patients with reactive airway disease, for which isoproterenol is no longer recommended).[11] (See Comments section.) In *adults* with advanced shock, >30 mcg/min has been reported.[3]
Additives	Contains 7 mg sodium chloride and 1 mg sodium metabisulfite for each 0.2 mg of isoproterenol.[3] See Appendix C for more specific information about potential adverse effects of sulfites.
Suitable diluents	NS, D5W,[3,21] D5LR, D5NS, LR,[21] D10W.[12]

Isoproterenol HCl

Maximum concentration	Usually 20 mcg/mL[3]; 64 mcg/mL has been used in extreme fluid restriction.[22]
Preparation and delivery	**Compatibility:** For PN compatibility information, please see Appendix D.
IV push	0.01–0.2 mg in *adults*.[3]
Intermittent infusion	Not indicated.
Continuous infusion	0.4–20 mcg/mL.[3,4,9] The Joint Commission recommends the use of standardized concentrations of vasoactive medications.[23]
Other routes of administration	In *adults*, IM or SC administration is recommended as initial therapy if time is not critical. Intracardiac injection may be used in extreme emergencies.[3]
Comments	**Significant adverse effects:** Risk factors for the development of arrhythmias include severe asthma, acidosis, and concomitant use of theophylline or corticosteroids.[3] Doses sufficient to increase the heart rate to more than 130 beats per minute (BPM) may increase the likelihood of inducing ventricular arrhythmias; consider reducing the rate or discontinuing the infusion if heart rate exceeds 110 BPM.[3] **Monitoring:** Systemic blood pressure, heart rate, urine output, ECG, as well as central venous pressure and blood gases should be closely monitored. Daily measurement of cardiac enzymes including CPK-MB is recommended when used in refractory asthma.[3] **Pharmacokinetic considerations:** Ten postoperative cardiac pediatric patients received doses of 0.029 ± 0.002 mcg/kg/min while nine with reactive airway disease received 0.5 ± 0.2 mcg/kg/min. Clearance was lower in the postoperative cardiac patients compared to those with reactive airway disease.[11] **Pharmacodynamic considerations:** Tolerance may occur following prolonged use.[3] **Other:** May be safer than isosorbide dinitrate or nitroglycerin for use during tilt table testing for syncope.[19,20]

Kanamycin Sulfate

Brand names

Generic

Medication error potential

None.

Contraindications and warnings

As with other aminoglycosides, kanamycin may cause auditory and renal toxicity.[1]

Aminoglycosides can cause neuromuscular blockade and potentiate the effects of neuromuscular blockers.[2] (See Appendix C for specific information.)

Contraindicated in patients with a history of aminoglycoside hypersensitivity.[1] Not indicated for long-term therapy.[1]

Infusion-related cautions

None.

Dosage

Inappropriate for mild-to-moderate infections.[3]

Although use has been questioned in pediatric patients, the following equation is recommended in *adult* obese patients receiving aminoglycosides: Dosing weight = IBW + 0.4 (TBW – IBW).[4–6] (See Appendix B.)

Neonates

PNA	<1200 g	1200–2000 g	≥2000 g
<7 days	15 mg/kg/day divided q 12 hr[7]*	15 mg/kg/day divided q 12 hr[7–10]	20 mg/kg/day divided q 12 hr[8–10]
≥7 days		20 mg/kg/day q 12 hr[8–10]	30 mg/kg/day divided q 8 hr[8–10]

*Until 4 weeks of age.

Infants and children: 15–30 mg/kg/day divided q 8–12 hr.[3,10] No information exists for once-daily kanamycin dosing.

Dosage adjustment in organ dysfunction

If CrCl is 10–50 mL/min, give normal dose q 24–72 hr; if CrCl is <10 mL/min, give q 48–72 hr.[11]

Maximum dosage

40–50 mg/kg/day, 500 mg/kg per course of therapy.[12] Daily *adult* dose is 1–1.5 g.[1,10] Larger doses or shorter dosing intervals of aminoglycosides are sometimes required in patients with cystic fibrosis,[13,14] major thermal burns or dermal loss,[15] ascites, or in patients with febrile granulocytopenia.[16] As with other aminoglycosides, individualize dosage based on serum concentrations.[1]

Additives

Contains 0.45% to 0.66% sodium bisulfite.[1,17] (See Appendix C for specific information about sulfite hypersensitivity.)

Suitable diluents

D5W or NS.[1,17]

Maximum concentration

5 mg/mL.[1,17]

Kanamycin Sulfate

Preparation and delivery	**Delivery system issues:** The mixing of kanamycin with a beta-lactam antibiotic in vitro can result in substantial inactivation of the aminoglycoside.[10,17] (See Appendix C for more specific information.) **Compatibility:** See Appendix D for PN compatibility information.[18]
IV push	Rapid infusion is not used.[1]
Intermittent infusion	2.5–5 mg/mL[1,17] infused over 30–60 minutes.[1,17]
Continuous infusion	Although aminoglycosides have been given by continuous infusion,[19,20] this method is not recommended. Toxicity occurs more frequently and the value of this administration method compared to intermittent infusion has not been established.[19,20]
Other routes of administration	May be given IM,[1,10,21] IT,[10] or IP.[1,17]
Comments	**Rare adverse effects:** Cochlear and/or vestibular ototoxicity has been associated with all aminoglycoside antibiotics.[1,10] Either total dose (>500 mg/kg)[12] or total AUC are better indicators of ototoxic risk than either peak or trough.[22,23] Aminoglycosides accumulate in renal cortical tissue and may damage proximal tubule cells leading to oliguric renal failure. This has been associated with elevated trough serum concentrations. Risk of nephrotoxicity may increase if aminoglycosides are combined with other potentially nephrotoxic drugs.[1] Use with caution when other drugs (e.g., macrolide antibiotics, loop diuretics, platinum-based chemotherapeutic agents) known to cause ototoxicity. **Monitoring:** Because large variability exists in patient response to therapy, individualize dosage based on serum concentrations, clinical response, and renal function. Although serum concentration monitoring has become routine practice in many institutions, not all patients receiving aminoglycosides require monitoring.[24,25] **Laboratory interference:** Serum concentrations may be falsely elevated when samples are collected through central venous silastic catheters.[26] Concomitant use with cephalosporins may falsely elevate creatinine.[1] **Osmolality:** The osmolality of a solution of 250 mg/mL ranged from 858–952 mOsm/kg depending on the testing method used.[17]

Ketamine HCl

Brand names	Ketalar, generic
Medication error potential	Look-alike, sound-alike drug names. Confusion has been reported between Ketalar and ketorolac.[1]
Contraindications and warnings	**Contraindications:** Known hypersensitivity to ketamine and those in whom a significant increase in blood pressure would result in harm.[2] **Warnings:** Does not impair laryngeal reflexes or independent airway maintenance; however, transient laryngospasm, apnea, and respiratory arrest have occurred.[3–5] Infants ≤3 months have a higher incidence of airway complications, leading some to recommend that ketamine be avoided in this age group.[3] Oxygen saturation should be monitored, and resuscitation and intubation equipment should be readily available for respiratory support.[2,6,7] Use with caution in patients at risk for increasing intracranial pressure.[2]
Infusion-related cautions	Rapid administration (<60 seconds) may result in increased pressor response and/or increased apnea and respiratory depression.[2] Emergence reactions (e.g., dream-like states, hallucinations, delirium) occur in ~12% of *adults*.[2] Of children who were premedicated with midazolam prior to ketamine, 1% of those <10 years of age and 4.2% of those ≥10 years of age experienced a severe emergence reaction.[8] Minimizing verbal, tactile, and visual stimulation after dosing decreases the likelihood of these reactions.[2] Short- or ultra-short acting barbiturates may be used as treatment.[2]
Dosage	Pretreatment with atropine or other drying agent prevents vagal-mediated bradycardia and decreases secretions.[2,6,7,9] **Anesthesia** **Induction** **IV:** 1–4.5 mg/kg.[2] **IM:** 5–13 mg/kg.[2,10] **Maintenance:** One-half to full induction dose repeated PRN[2] or 1–5 mg/kg/hr.[2,11] **Adjunct to intubation:** 1–2 mg/kg IV.[6] **Procedural sedation/analgesia:** Usually IV doses of 0.25–5 mg/kg and IM doses of 0.5–13 mg/kg are used for nonsurgical procedures.[3,6,12,13] In 32 children undergoing muscle biopsy, 2 mg/kg IV repeated in 10 minutes if needed or 10 mg/kg IM was used.[14] In the ED, 3–4 mg/kg IM has been used.[9,15–17] For emergencies, the AAP recommends 1–2 mg/kg IM or 0.5–1 mg/kg IV.[6] One group reported using an IV loading dose of 1 mg/kg followed by 50–75 mcg/kg/min for the procedure's duration.[4] Small doses of ketamine were added to propofol total IV anesthesia used for radiation therapy in seven pediatric oncology patients to prevent emergence agitation associated with propofol. Prior to the addition of ketamine, all of the patients had experienced emergence agitation during a previous anesthetic session. Patients received a mean loading dose of 1.3 mg/kg (range 0.35–6.56 mg/kg) followed by a mean continuous infusion of 37 mcg/kg/min (range 10–132 mcg/kg/min) for a total of 123 anesthetic sessions. There were no recurrences of emergence agitation in any of the patients after the addition of ketamine.[18]

Dosage *(cont.)*	**Other uses** **Sedation in the ICU:** After cardiac surgery, 10 children were given 16.6–33.3 mcg/kg/min (1 or 2 mg/kg/hr) for 24 hours.[19] Others report doses of 0.5–1 mg/kg followed by 10 mcg/kg/min for 48–72 hours.[20] **Severe bronchospasm:** An 8-month-old received 2 doses of 1.4 mg/kg 10 minutes apart followed by 3.33 mcg/kg/min (0.2 mg/kg/hr) that was weaned over 40 hours.[21] The other cases reviewed also improved with bolus doses of 0.5–4.8 mg/kg and three of these also received a continuous infusion of 16.6–42 mcg/kg/min (1 or 2.5 mg/kg/hr) for 8–24 hours.[21] A separate retrospective review identified 17 mechanically ventilated children who improved with bolus doses of 2 mg/kg followed by a continuous infusion of 20–60 mcg/kg/min for 12–96 hours.[22] Mechanical ventilation was avoided in two children with severe asthma who were given 2 mg/kg followed by 33.33–50 mcg/kg/min (2–3 mg/kg/hr).[23] **Opioid withdrawal:** A 2-year-old (9.5-kg) toddler who failed traditional fentanyl weaning strategies was started on ketamine at 17.5 mcg/kg/min (10 mg/hr). The fentanyl was successfully weaned off and then the ketamine was weaned.[24]
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal insufficiency.[25,26] Prolonged effects may be observed in patients with liver disease. Consider dose reductions in patients with hepatic impairment.[9]
Maximum dosage	Not established. Large doses prolong recovery and increase the risk of adverse events. IV doses up to 11 mg/kg and IM doses up to 17 mg/kg have been used during surgery.[3]
Additives	0.1 mg/mL benzethonium chloride.[27]
Suitable diluents	SW, D5W, or NS.[2,27]
Maximum concentration	50 mg/mL for IV push.[2]
Preparation and delivery	**Preparation:** The 100-mg/mL concentration must be diluted with an equal volume of SW, D5W, or NS before infusion.[27] **Stability:** Intact vials should be stored at room temperature. Ketamine is a colorless to slightly yellow solution. Do not use if a precipitate is present.[27] Storage in polypropylene syringes did not result in a loss of potency.[27] **Compatibility:** Incompatible with barbiturates and diazepam.[2] **Photosensitivity:** Protect from light. Although the drug may darken upon prolonged exposure to light, this darkening does not affect potency.[27]
IV push	Over 60 seconds not to exceed 0.5 mg/kg/min or 2 mg/min in *adults.*[2] The dose may be repeated to maintain anesthesia.
Intermittent infusion	Not indicated.

Ketamine HCl

Continuous infusion

May be given by continuous infusion.[2,27,28]

A 12-year-old female with severe pain due to a cervical spinal tumor received a test dose of 7.5 mg ketamine followed by a continuous infusion ranging from 36–410 mg/24 hr. She received long-term therapy for 67 days in a home-care setting.[29]

Other routes of administration

IM.[2,16,17,30,31] Laryngospasm was more common with IM compared to IV ketamine.[31]

Caudally administered ketamine (in addition to local anesthetic) has been used to reduce analgesic requirements in patients undergoing urological, lower abdominal, or lower limb surgery.[32]

Comments

Adverse effects: The vomiting associated with ketamine is not related to the initial dose, but it may be increased in those receiving larger cumulative doses.[33] In one study, the incidence of vomiting in 128 children receiving ketamine alone was 12.6% and in 127 children receiving concomitant ondansetron was 4.7%.[13] Ketamine used with midazolam resulted in fewer respiratory adverse events but more vomiting than midazolam and fentanyl.[34] Similarly, combining ketamine with propofol resulted in fewer episodes of hypotension and bradycardia but more agitation than propofol alone.[12]

A previously healthy 8-year-old female developed severe neurogenic pulmonary edema following an IM dose of 6.25 mg/kg for dressing changes of first-degree burns.[35]

Drug interactions: Substrate for CYP 450 isoenzymes 2B6, 2C9, and 3A4.[36]

Ketorolac Tromethamine

Brand names	Generic
Medication error potential	Look-alike, sound-alike drug names. Confusion has been reported between ketorolac and Ketalar and methadone, and Toradol was confused with Foradil.[1]
Contraindications and warnings	**U.S. boxed warning[2]:** Ketorolac is indicated for the short-term (≤5 days) management of moderately severe acute pain that requires opioid analgesia, usually in a postoperative setting. Patients should be switched to alternative analgesics as soon as possible, but ketorolac administration should not exceed 5 days. May increase the risk of serious GI toxicities including inflammation, ulceration, bleeding, and perforation of the stomach or intestines, which may be fatal. (See Comments section.) **Contraindications:** Contraindicated in patients with (1) previous hypersensitivity to ketorolac, aspirin, or other nonsteroidal anti-inflammatory drug (NSAID); (2) with active peptic ulcer disease, recent GI bleeding/perforation, or history of peptic ulcer disease or GI bleeding; (3) with advanced renal impairment and in patients with risk for renal impairment due to hypovolemia; (4) with suspected/confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, before any major surgery and intraoperatively, and others at high risk of bleeding; (5) undergoing coronary artery bypass graft surgery perioperatively; (6) IT or epidural administration (alcohol content), labor and delivery, nursing mothers, concomitant probenecid, concomitant pentoxifylline, concomitant aspirin, or other NSAID use.
Infusion-related cautions	Anaphylactic reactions may occur in patients with a history of hypersensitivity to other NSAIDs, including aspirin, or in patients with nasal polyps, asthma, angioedema, or bronchospastic reactions of the histamine-dependent type.[23]
Dosage	Ketorolac has been used concomitantly with morphine and meperidine and is opioid-sparing effect. *Therapy (parenteral and oral) should not exceed 5 days.* **Analgesia/pain management** *The manufacturer recommends single-dose therapy (≤30 mg IM or 15 mg IV) for those weighing <50 kg.*[2] **Surgery/procedures:** The use of a smaller dose (0.5 mg/kg) has been recommended.[4–6] 0.5–1 mg/kg have been given to infants ≥1 month and children after induction of general anesthesia, at the beginning of a procedure, 30 minutes before the end of surgery/procedure, or immediately postoperative.[4–19] One study in neonates gave 1 mg/kg.[20] **Multidose therapy:** 0.5 mg/kg q 6 hr.[3,4,11,21] A loading dose of 1 mg/kg can be given prior to beginning scheduled dosing.[3,21] One study in neonates, infants, and children supported the postsurgical use of 0.5 mg/kg q 8 hr for 1–2 days.[22] While the manufacturer's labeling limits therapy to ≤5 days,[2] early clinical experience with ketorolac in children reported the use of 0.17–1 mg/kg q 4–6 hr for an average length of 3.4 days (range 1–12) and up to 31 doses.[21] **Antipyretic:** 0.5–1 mg/kg as a single dose.[21,23]

Dosage *(cont.)*	**Other uses** **Postoperative bladder spasms (after ureteral reimplantation):** 0.5 mg/kg q 6 hr for 48 hours reduced the frequency and severity of spasms.[24] One study reported using 0.5 mg/kg followed by 83.3 mcg/kg/hr in 26 children aged 1–5 years and found ketorolac was more effective in reducing frequency of bladder spasms and need for rescue analgesia compared to fentanyl.[25] **Migraine headaches:** 0.5 mg/kg was inferior to prochlorperazine.[26] **Sickle cell vaso-occlusive pain crisis:** 0.9 mg/kg did not reduce the total morphine dose required.[27] (See Comments section.) **Complex regional pain syndrome:** IV regional anesthesia using 0.5 mg/kg (and lidocaine) in an 11-year-old and a 15-year-old.[28]
Dosage adjustment in organ dysfunction	If CrCl is 10–29 mL/min, give 50% of the usual dose, and if CrCl is <10 mL/min, give 25% to 50% of the usual dose.[29]
Maximum dosage	A single dose of 30 mg (IM) or 15 mg (IV) in children.[2] A single loading dose of 60 mg was administered to a 16-year-old.[21] A single IV dose of 60 mg was administered preoperatively in patients undergoing single-stage adjustable strabismus surgery, which included patients >10 years of age; mean age 21.28 ± 14.04 years.[30]
Additives	**15 mg/mL (IV or IM use):** 10% (w/v) ethanol, 6.68 mg/mL NaCl.[2] **30 mg/mL (IV or IM use):** 10% (w/v) ethanol, 4.35 mg/mL NaCl.[2] **60 mg/2 mL (IM use only):** 10% (w/v) ethanol, 8.7 mg/mL NaCl.[2]
Suitable diluents	D5NS, D5W, LR, R, NS.[31]
Maximum concentration	30 mg/mL for IV infusion.[2] 60 mg/2 mL is intended for IM use only.[2]
Preparation and delivery	Incompatible in a syringe with morphine, meperidine, promethazine, and hydroxyzine.[2, 31]
IV push	Over ≥15 seconds[2] to over 1–5 minutes in children.[21]
Intermittent infusion	Not indicated.
Continuous infusion	May be given by continuous infusion (recommended 0.17 mg/kg/hr in children).[3]
Other routes of administration	IM.[2] IV is the preferred route in children due to pain associated with IM administration.[3,21]

Ketorolac Tromethamine

Comments

Adverse effects

Bleeding: Ketorolac was considered a contributing factor to hematuria in a 16-year-old and to incision-site bleeding in an 11-year-old child.[21]

A retrospective review of 57 postsurgical neonates (0–3 months) concluded that infants <21 days and <37 weeks calculated gestational age are at increased risk for bleeding and that ketorolac should be avoided in this population.[32]

While post-tonsillectomy patients receiving 1 mg/kg of ketorolac had fewer emetic episodes than those given 0.1 mg/kg/dose of morphine, they had more major bleeding.[8] More measures to control bleeding were also noted post-tonsillectomy in children receiving ketorolac (1 mg/kg) compared to those receiving 35 mg acetaminophen/kg rectally.[7]

Renal dysfunction: Acute renal failure associated with ketorolac administration has been reported in infants and children.[33–35] One study reported development of irreversible renal failure in a 17-year-old in sickle cell crisis, despite adequate hydration and recommends following administration guidelines for renal comprised patients and monitoring renal function closely.[35]

Pharmacokinetics: A study in 36 children and another in 17 infants found that an IV dose of 0.5 mg/kg resulted in similar concentrations over a 6-hour period as that reported for *adults*.[5,36] The pharmacokinetic parameters were not different among ages 1–3 years, 4–7 years, 8–11 years, and 12–16 years.[5] Another study in 14 infants aged 2–6 months reported similar clearance of single doses of 0.5 mg/kg and 1 mg/kg as compared to patients aged 6–18 months.[19] The IV and IM bioavailability and efficacy are comparable.[37]

Opioid-sparing: A study evaluating 19 infants <6 months of age postcardiothoracic surgery found that ketorolac was safe, but that it did not decrease the requirement for standard analgesia.[38] However, another study in children 1–5 years of age postinguinal hernia repair noted that a preoperative dose of 1 mg/kg (along with 20 mg/kg of IV acetaminophen) was safe, effective, and reduced the need for rescue analgesics (i.e., fentanyl).[39]

L-cysteine HCl

Brand names	Various manufacturers
Medication error potential	None reported.
Contraindications and warnings	**Contraindications:** Hypersensitivity to cysteine or any component.[1] Should not be used in patients with hepatic coma or metabolic disorders that impair nitrogen metabolism.[1] **Warnings:** Metabolic acidosis, primarily in neonates, has been reported and relates to the "hydrochloride" component of cysteine.[2,3] Each 1 mmoL cysteine (175 mg) delivers 1 mEq chloride and 1 mEq hydrogen ion. In order to account for the extra hydrochloride ions and prevent acidosis, add 1 mEq acetate electrolyte salt for each mmoL (175 mg) of cysteine to the PN solution. Contains aluminum, which may reach toxic levels with prolonged parenteral administration if kidney function is impaired.[1] Premature neonates are at increased risk for toxicity due to kidney immaturity. They also require large amounts of calcium and phosphate solutions, which also contain aluminum.
Infusion-related cautions	Peripheral infusion of amino acids may result in local reactions (e.g., warm sensation, erythema) and phlebitis or thrombosis at the infusion site.[1] The pH of L-cysteine HCl is about 1–2.5.[1]
Dosage	L-cysteine HCl is added to PN solutions formulated with pediatric amino acids in order to normalize plasma amino acid patterns in infants[2,4] and has been added to PN solutions formulated with standard amino acid solutions to acidify the solution and enhance calcium and phosphorous solubility.[5] 30–40 mg/g of pediatric amino acid[1,4,6] or 0.4–1 mmoL/kg (~48–121 mg/kg).[2,3] The American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) has recommended alternate dosing during PN product shortages as follows[7]: Restrict supplementation in PN to neonates $\leq$1 kg and neonates $>$1 kg at risk for L-cysteine deficiency (postsurgical neonates or neonates with sepsis). When L-cysteine is not added to PN solutions, calcium and phosphorus solubility should be re-evaluated to insure that a precipitate will not develop due to increased solution pH.[7] Calcium–phosphorus solubility data exist for PN solutions without L-cysteine.[8]
Dosage adjustment in organ dysfunction	Decrease the overall amino acid dose in patients with renal dysfunction and hepatic insufficiency.[1] In these cases, dose using mg of L-cysteine/g pediatric amino acids is appropriate because it is based on the grams of amino acids provided and not on the patient's weight. Contains aluminum, which may reach toxic levels with prolonged parenteral administration if kidney function is impaired.[1]
Maximum dosage	Should be based on mg/g pediatric amino acids. 30 mg/g in those prescribed 3 g/kg and 40 mg/g in those prescribed 2.5 g/kg results in a dose of 90 or 100 mg/kg, respectively.[1,4,6] Doses of 121 mg/kg have been used.[2,3]
Additives	L-cysteine hydrochloride monohydrate contains 5.7 mEq Cl/g of L-cysteine HCl. Contains aluminum as a contaminant.[1]
Suitable diluents	PN solutions.
Maximum concentration	Dependent on volume of PN solution.

L-cysteine HCl

Preparation and delivery	**Stability:** Store at controlled room temperature 15°C to 30°C.[1] Do not freeze.[1] L-cysteine HCl should be added to the PN solution just prior to infusion.[1]
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	Given via PN solution.
Other routes of administration	Not indicated.
Comments	**Adverse effects:** Aluminum is a contaminant of this product. Premature neonates who receive 4–5 mcg/kg/day of aluminum parenterally may accumulate aluminum at levels associated with CNS and bone toxicity.[9] **Miscellaneous:** L-cysteine exists in equilibrium with its dimer, cystine, and the extent of dimerization depends on pH. 1 mmol = 121 mg of cysteine/cystine. Studies have suggested that cysteine biosynthesis may be intact in preterm infants >32 weeks gestational age, fed both enterally or via PN, assuming adequate sulfur amino acid intake.[6,10–12]

Labetalol HCl

Brand names	Trandate injection, generics
Medication error potential	High-alert medication (adrenergic antagonist) that has an increased risk of causing significant patient harm if it is used in error.[1] There are significant differences between IV and oral dosing.[2] The rate of administration of continuous IV infusions is different for pediatric patients (mg/kg/hr) versus *adults* (mg/min).[2]
Contraindications and warnings	**Contraindications:** Hypersensitivity to labetalol or any component. Patients with asthma, obstructive airway disease, cardiogenic shock, uncompensated congestive heart failure, severe bradycardia, heart block (except in patients with a functioning artificial pacemaker); in conditions associated with severe and prolonged hypotension.[3] Caution in patients with hyper-reactive airway disease or bronchospastic disease, diabetes mellitus, compensated heart failure, hepatic impairment, peripheral vascular disease and Raynaud disease, history of psychiatric illness, myasthenia gravis, and pheochromocytoma.[3] **Warnings:** Symptomatic hypotension with or without syncope can occur and cerebral and cardiac adverse events (infarction/ischemia) may occur if blood pressure decreases too rapidly. Initiate therapy with a low dose and slowly titrate up to decrease episodes of syncope and hypotension. Severe hepatic injury has been rarely reported; periodically monitor liver function tests with prolonged use.[3] Reversible myopathy, consistent with rhabdomyolysis, has been reported in two pediatric patients and in the *adult* literature; monitor for potentially severe toxic myopathy.[4]
Infusion-related cautions	Orthostatic hypotension may occur with IV administration, so patients should remain supine during administration and for up to 3 hours after the infusion is complete.[3]
Dosage	**Intermittent infusion:** 0.2–1 mg/kg[5–11] over 2–3 minutes (max 2 mg/min) up to 40 mg.[2] The dose can be repeated at 10-minute intervals to a maximum of 3–4 mg/kg up to a total dose of 300 mg.[5] The maximum hypotensive effect usually occurs within 5–15 minutes after injection.[3] **Continuous infusion:** 0.25–3 mg/kg/hr titrated to blood pressure.[5–7,12,13] Thirteen children (9.2 ± 3.7 years of age, mean ± SD) received IV labetalol for treatment of hypertension. Labetalol was shown to effectively lower blood pressure with a mean initial dose of 0.55 ± 0.34 mg/kg followed by a continuous infusion of 0.78 ± 0.39 mg/kg/hr.[7] In a retrospective study, 41 children were treated with labetalol continuous infusions (25 labetalol monotherapy, 16 combination therapy with sodium nitroprusside) for hypertensive emergencies. Doses of 1–3 mg/kg/hr were reported to safely and effectively control blood pressure in these patients.[12] Fifteen infants and small children (≤24 months of age) were treated with a continuous infusion of labetalol for hypertensive crisis. A mean dose of 0.44 ± 0.2 mg/kg/hr produced a marked improvement in blood pressure within the first 6 hours of infusion initiation. A breakpoint for dose saturation was reported at 0.59 mg/kg/hr.[13]
Dosage adjustment in organ dysfunction	Dosage reduction may be necessary in patients with hepatic impairment.[3] No adjustment required for renal impairment.[14]
Maximum dosage	1 mg/kg/dose up to 40 mg.[6] A cumulative dose of 3–4 mg/kg per event and up to 300 mg per event.[5] Continuous infusion up to 3 mg/kg/hr have been used.[12]

Labetalol HCl

Additives	Anhydrous citric acid and sodium hydroxide as necessary (for pH adjustment) and edetate disodium.[3,14] Some products contain methyl and/or propyl parabens as preservatives.[3] (See Appendix C for specific information about parabens, potential for toxicity.)
Suitable diluents	D5W, D5LR, D5NS, D5¼NS, D5⅓NS, D2.5½NS, LR, NS.[3,14]
Maximum concentration	5 mg/mL for IV injection[2] and 1 mg/mL for continuous infusion.[14] Undiluted solution (5 mg/mL) has been given for continuous infusion to a small number of *adult* patients who were extremely fluid restricted.[2]
Preparation and delivery	**Stability:** May be stored at room temperature or under refrigeration and should be protected from freezing. The solution is clear to slightly yellow. According to product labeling, labetalol is physically compatible and stable in all listed suitable diluents for 24 hours refrigerated or at room temperature.[3] Others report stability for up to 72 hours refrigerated or at room temperature.[14] **Compatibility:** Incompatible with sodium bicarbonate.[14] **Photosensitivity:** Should be protected from light.[3]
IV push	5 mg/mL[3] (commercially available) given over 2–3 minutes, not to exceed 2 mg/min.[14]
Intermittent infusion	Not administered by this method.
Continuous infusion	1 mg/mL.[14]
Other routes of administration	None reported.
Comments	**Laboratory interference:** Labetalol metabolites in the urine may cause falsely elevated concentrations of urinary catecholamines (e.g., metanephrine, normetanephrine, vanillylmandelic acid) when measured by fluorimetric or photometric methods. When screening labetalol-treated patients suspected of having pheochromocytoma or when evaluating those with the tumor, specific assay methods such as high-performance liquid chromatography with solid phase extraction should be used.[3] Labetalol may produce a false–positive amphetamine test when urine is screened using the Toxi-Lab A or Emit-d.a.u. assays.[3]

Lacosamide Injection

Brand names	Vimpat
Medication error potential	None reported.
Contraindications and warnings	Not recommended in severe hepatic impairment.[1] Use cautiously in patients with known cardiac conduction problems (e.g., second-degree atrioventricular [AV] block), who are taking drugs known to prolong the PR interval, or in those with severe cardiac disease.[1] May cause syncope.[1] Do not discontinue abruptly, but gradually withdraw to minimize the potential of increased seizure frequency.[1] Multiorgan hypersensitivity reactions have been reported.[1]
Infusion-related cautions	One report of bradycardia has been noted during a 15-minute infusion in a patient concurrently receiving a beta-blocker. Heart rate rapidly returned to normal upon discontinuation of lacosamide.[1] Infusion site reactions including injection site pain or discomfort, irritation, and erythema may occur.[1]
Dosage	IV lacosamide is FDA-labeled as adjunctive therapy for partial-onset seizures in patients with epilepsy who are 17 years and older when oral administration is temporarily not feasible.[1] IV and oral administration is equivalent in dose and frequency.[1,2] When switching from oral therapy, the initial total daily IV dosage should be equivalent to the total daily dosage and frequency of oral lacosamide and should be infused intravenously over a period of 30–60 minutes.[1] ***Adults:*** Although it is not FDA-approved for status epilepticus or refractory status epilepticus, it has been successfully used in the management of refractory status epilepticus in *adults*.[3–9] Most of these patients received 200–400 mg as a loading dose followed by 200 mg q 12 hr. There is experience with IV BID infusion for up to 5 days.[1] Lacosamide-controlled status epileptics in 75% to 100% of *adults*.[5] Conversely, an observational case series of nine *adults* admitted to the ICU with refractory status epileptics (after failure of at least two other agents) failed to respond to IV lacosamide 200 mg followed by 200 mg q 12 hr.[4] **Pediatrics:** The efficacy and safety of lacosamide in *adults*, and the occasional shortage of other parenteral anticonvulsants, has led clinicians to consider lacosamide for children with refractory status epilepticus. Although it has been given orally in pediatric patients (as young as 1 year of age) for adjunctive therapy for refractory partial-onset seizures (including Lennox-Gastaut syndrome [LGS])[10–13] and orally for refractory status epileptics,[14] there is insufficient information regarding dosing, efficacy, and safety of the parenteral product in pediatric patients with refractory convulsive or nonconvulsive status epileptics. Since dosing with oral and IV therapy are equivalent, this information may assist practitioners who decide to try IV lacosamide for refractory status epilepticus. **Oral dose in adjunctive therapy for partial onset seizures:** Lacosamide has been given to patients ranging in age from 1–18 years of age.[10–13] Doses of 2.4–14.7 mg/kg/day,[13] 1.3–4.7 mg/kg/day divided BID,[11] 1.7–10 mg/kg/day divided BID,[10] and 20 mg/kg/day divided BID.[12] **Refractory status epilepticus:** An 8-year-old boy with refractory status epilepticus, which had persisted for 10 weeks, received oral lacosamide (25 mg BID). The number of seizures decreased within 3 days and stopped within 5 days.[14] A 17-year-old was given IV lacosamide for either seizure clusters or refractory status epilepticus.[5] *Adult* patients in the study who had status epilepticus received an initial loading dose of 200–400 mg followed by a median of 200 mg (200–400 mg).[5]

Lacosamide Injection

Dosage adjustment in organ dysfunction	No adjustment is necessary in those with mild-to-moderate renal impairment.[1] If CrCl is <30 mL/min in *adults,* the dose should not exceed 300 mg/day.[1] Because lacosamide is removed by a 4-hour hemodialysis session, a supplemental dose (up to 50%) should be given after dialysis.[1] The maximum dose in *adults* with mild-to-moderate hepatic impairment is 300 mg/day.[1] Use is not recommended in those with severe hepatic impairment.[1]
Maximum dosage	Not established. 600 mg/day[15] orally and 400 mg[5] intravenously in *adults* and 20 mg/kg/day divided BID in pediatrics.[12]
Additives	Hydrochloric acid is used to adjust pH from 3.5 to 5.[1] Any unused portion should be discarded, as the product does not contain a preservative.[1]
Suitable diluents	NS, D5W, LR.[1]
Maximum concentration	10 mg/mL (commercially available).[1]
Preparation and delivery	May be given undiluted.[1] When mixed in suitable diluent and placed in glass or PVC bag, it is stable for 24 hours at room temperature (15°C to 30°C).[1] If particulate matter or discoloration noted, the product should not be used.[1] Any unused portion should be discarded, as the product does not contain a preservative.[1]
IV push	Not recommended.
Intermittent infusion	Infuse over 30–60 minutes.[1] Some have given at rates of 60 mg/min[5] up to 80 mg/min in *adults*.[7]
Continuous infusion	No reports of administration by this method.
Other routes of administration	No reports of administration by other methods.
Comments	May produce a dose-related increase in the PR interval or cause AV block.[1,15,16] This effect is likely the result of lacosamide enhancement of slow inactivation of voltage-gated sodium channels. IV loading doses of 400 mg in *adults* were associated with dizziness, somnolence, and nausea.[17] Angioedema has been noted in *adults* following 2 doses of IV lacosamide and later in the course of therapy.[4] Lacosamide may worsens seizures in those with LGS.[18]

Leucovorin Calcium

Brand names

Wellcovorin, generic

Medication error potential

ISMP and USP reports that leucovorin has been confused with Leukeran and levothyroxine and patient harm did not occur.[1,2]

Contraindications and warnings

Contraindications: Hypersensitivity to leucovorin or product components; use as therapy for pernicious anemia and other megaloblastic anemias secondary to lack of vitamin B_{12}.[3,4]

Do not administer intrathecally; harm or fatality may result.[3,4]

Warnings: Administer promptly in the treatment of accidental overdose of folic acid antagonists; as the time interval between antifolate administration and leucovorin rescue increases, leucovorin effectiveness decreases. Higher doses of leucovorin or prolonged administration of leucovorin may be indicated when delayed methotrexate excretion is due to third-space fluid accumulation, renal insufficiency, or inadequate hydration.[3,4]

IV administration is recommended for doses >25 mg due to saturation of oral absorption with larger doses.[5]

Methotrexate concentrations should be monitored closely to determine the appropriate dose and duration of leucovorin rescue. (See Methotrexate monograph.)

Infusion-related cautions

None.

Dosage

Refer to individual protocol.

Leucovorin rescue after high-dose (12–15 g/m²) methotrexate[3,4]: 10 mg/m² IV q 6 hr for 72 hours starting 24 hours after the beginning of the methotrexate infusion. Dosing should be continued (in tandem with hydration and urinary alkalization) until methotrexate level is $<5 \times 10^{-8}$ M (0.05 micromolar [μM]). Leucovorin dosing should be adjusted based on methotrexate serum concentrations as below:

	Laboratory Findings	Leucovorin Dosage
Normal methotrexate elimination	Serum methotrexate level 10 μM at 24 hr after administration, 1 μM at 48 hr, and <0.2 μM at 72 hr	10 mg/m² mg IV q 6 hr for 72 hr
Delayed-late methotrexate elimination	Serum methotrexate level >0.2 μM at 72 hr, and >0.05 μM at 96 hr after administration	Continue 10 mg/m² IV q 6 hr until methotrexate level is <0.05 μM
Delayed-early methotrexate elimination and/or evidence of acute renal injury	Serum methotrexate level of ≥50 μM at 24 hr, or ≥5 μM at 48 hr after administration; OR a 100% or more increase in SCr level at 24 hr after methotrexate administration	100 mg/m² IV q 3 hr until methotrexate level <1 μM; then 10 mg/m² IV q 3 hr until methotrexate level <0.05 μM

Dosage *(cont.)*

Alternative leucovorin rescue after high-dose methotrexate (based on 48-hour serum concentration)[6]:

48-hr Methotrexate Level	Leucovorin Dose (IV)
≥80 µmol/L	1000 mg/m² q 6 hr
≥8 to <80 µmol/L	100 mg/m² q 3 hr
≥2 to <8 µmol/L	10 mg/m² q 3 hr
≥0.1 to <2 µmol/L	10 mg/m² q 6 hr

Methotrexate overdose: 10 mg/m² IM/IV q 6 hr until serum methotrexate level is $<10^{-8}$ M. If 24-hour SCr has increased 50% over baseline or if 24-hour methotrexate level is $>5 \times 10^{-6}$ M or the 48-hour level is $>9 \times 10^{-7}$, increase leucovorin dose to 100 mg/m² IV q 3 hr until methotrexate level is $<10^{-8}$ M.[3,4]

Folate deficient megaloblastic anemia: ≤1 mg/day IM/IV.[3,4]

Megaloblastic anemia secondary to congenital deficiency of dihydrofolate reductase: 3–6 mg daily IM.[5]

Methanol toxicity cofactor therapy: 1 mg/kg (maximum dose 50 mg) IV q 4–6 hr. Administer over 30–60 minutes. Continue until methanol and formic acid are completely eliminated.[7]

Dosage adjustment in organ dysfunction

See Dosage section.

Maximum dosage

1000 mg/mg².[3,4]

Additives

Each mL contains 8 mg sodium chloride, sodium hydroxide, and/or hydrochloric acid.[3,4]

Each mg of leucovorin contains 0.004 mEq of calcium.[3,4]

Suitable diluents

Reconstitution: BW, SW.[3,4,8]

Dilution: D5W, NS.[8]

Maximum concentration

20 mg/mL.[3,4,8]

Preparation and delivery

The lyophilized powder is reconstituted with BW or SW.[3,4,8] When doses >10 mg/m² are needed, avoid use of diluents containing benzyl alcohol.[8]

IV push

Administer over 15 minutes.[5] Infuse at maximum rate of 160 mg/min.[3,4]

Intermittent infusion

Infuse at maximum rate of 160 mg/min.[3,4]

Continuous infusion

Has been used as part of a combination regimen with fluorouracil as continuous infusion over 24–48 hours in treatment of colorectal and other cancers in *adults*.[9–12]

Leucovorin Calcium

Other routes of administration	Not recommended. (See Contraindications in the Contraindications and Warnings section.)
Comments	Patients who have exhibited delayed-early methotrexate elimination with high-dose methotrexate are more likely to develop reversible renal failure. Closely monitor fluid and electrolyte status. Leucovorin rescue should be extended for an additional 24 hours (14 doses over 84 hours) in subsequent courses of therapy.[3,4] **Adverse effects:** Allergic sensitization, including anaphylaxis and urticarial, has been reported after administration of leucovorin.[3,4] **Monitoring:** CBC with differential; plasma methotrexate concentrations, SCr.[3–5] **Drug interactions:** Leucovorin may decrease serum concentrations of fosphenytoin, phenobarbital, phenytoin, and primidone.[3–5] Leucovorin may enhance the toxicity of 5-fluorouracil. May decrease the therapeutic effect of trimethoprim when used for the treatment of *Pneumocystis jiroveci*.[5] Glucarpidase may decrease serum concentrations of the active metabolite of leucovorin; avoid leucovorin administration within 2 hours of glucarpidase dosing. (See Glucarpidase monograph.)

Levetiracetam

Brand names	Keppra
Medication error potential	Look-alike, sound-alike drug names. Confusion with lamotrigine, levocarnitine, Kaletra, Keflex, and levofloxacin has been reported.[1] Confusion with levofloxacin has resulted in patient harm.[1]
Contraindications and warnings	**Contraindications:** Hypersensitivity to levetiracetam or any component of the formulation.[2] **Warnings:** Severe dermatologic reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome, have been reported in children and *adults.*[2] Onset generally occurs within ~2 weeks of initiation but may be delayed more than 4 months. Levetiracetam should be discontinued if signs of a hypersensitivity reaction or unspecified rash occur. Anticonvulsants should not be discontinued abruptly because of the possibility of increasing seizure frequency.[2] Neuropsychiatric adverse events including somnolence, fatigue, coordination difficulties, behavioral abnormalities (e.g., aggression, agitation, anxiety, anger, hostility, irritability, depression) and psychotic symptoms (e.g., psychosis, hallucinations) may occur.[2,3] Behavioral abnormalities may occur more frequently in children and may required dosage reductions.[2] The incidence of suicidal behavior/ideation is greater than placebo (0.43% versus 0.24% risk) in patients receiving anticonvulsants, including levetiracetam, as either monotherapy or as adjuvant therapy for the treatment of epilepsy, psychiatric disorders, and other conditions.[2] The symptoms were observed as early as 1 week after initiation of antiepileptic drugs and continued through duration of trials (most trials ≤24 weeks). Risk did not vary significantly by age (age range: 5–100 years). Patients should be monitored for emergence of suicidal thoughts or behavior, thoughts of self-harm, any unusual changes in behavior or mood, or the emergence or worsening of depressive symptoms.
Infusion-related cautions	None reported.
Dosage	Labeled as replacement therapy for patients >16 years of age who have been on oral therapy but cannot temporarily tolerate oral medications.[2] **Naive patient (no previous levetiracetam)** **Neonatal seizures:** IV levetiracetam has been given to patients as young as 3 weeks,[4] 1 month,[5,6] 2 months,[7] and 3 months.[3] Limited information available for neonatal seizures.[8] Loading dose of 20–50 mg/kg[9–13] followed by maintenance doses of 5–10 mg/kg/day[13] or 20–60 mg/kg/day divided q 12 hr.[9–12] Patients with extensive intracerebral hemorrhage may be less responsive to therapy.[11] **Infants and children**[3–7,14–17] **Loading dose:** 8.8 mg/kg (mean; n = 7),[3] 60 mg/kg (n = 2),[6] 22 mg/kg (mean, n = 10),[5] and 50 mg/kg (n = 9).[7] The largest study to date involved 45 children who were given a mean dose of 14 mg/kg (range: 5–30 mg/kg).[15] **Maintenance dose:** 36.1 mg/kg/day (range: 5–92 mg/kg/day) divided q 12 hr (n = 7),[3] 50 mg/kg/day divided q 12 hr,[7] and 60 mg/kg/day divided q 12 hr.[6] One study gave 20–40 mg/kg/dose q 8 hr in infants.[4]

Dosage *(cont.)*	**Adolescents and *adults***
	Loading dose: 50 mg/kg/dose (maximum dose: 2500 mg).
	Maintenance dose: 30–55 mg/kg/day divided BID. Efficacy of doses other than 3000 mg/day has not been established.
	Replacement therapy (prior levetiracetam)[3,4,6,7]: The initial total daily IV dosage should equal the total daily dosage and frequency of oral levetiracetam.[2] Although mean doses have ranged from 5–120 mg/kg/day,[3,4,6,7] most patients received 50–60 mg/kg/day divided q 12 hr.[4,6,7] One study gave 20–40 mg/kg/dose q 8 hr in infants.[4]
	The patient may be switched to oral levetiracetam at the same daily dosage and frequency as that administered intravenously.[2]
Dosage adjustment in organ dysfunction	If CrCl is <50 mL/min/1.73 m^2, give 50% of the normal dose[18]; in *adults* with moderate renal dysfunction (30–50 mL/min/1.73 m^2), give 250–750 mg q 12 hr and 250–500 mg q 12 hr if CrCl <30 mg/mL/1.73 m^2.[2]
	Patients on hemodialysis, continuous ambulatory peritoneal dialysis, or continuous renal replacement therapy should receive 50% of normal dose every 24 hours[18]; a supplemental dose after hemodialysis is recommended.[18]
	Pharmacokinetics parameters were unchanged in mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment.[2] Total body clearance was half that of normal subjects compared to those with severe hepatic impairment (Child-Pugh C).[2] No dose adjustment is needed for patients with hepatic impairment.[2] (See Other in the Comments section.)
Maximum dosage	Loading dose of 70 mg/kg[7] 120 mg/kg/day[4] up to 3 g/day.[2]
Additives	None reported.
Suitable diluents	NS, LR, or D5W.[2]
Maximum concentration	1500 mg (3 × 5 mL vials) should be diluted in 100 mL of compatible diluents.[2] Others have safely used a 1:1 dilution of drug from vial with D5W or NS.[19]
Preparation and delivery	**Preparation:** Vial must be diluted prior to use. Do not dilute premixed 100-mL bag.
	Stability: Intact vials should be store at 25°C. Reconstituted and prefill products are stable for at least 24 hours at room temperature (15°C to 30°C).[2] Product with particulate matter or discoloration should not be used.[2] Any unused portion of a vial should be discarded as the product does not contain preservative.[2]
IV push	Not used.
Intermittent infusion	Over 15 minutes.[2] Doses as large as 60 mg/kg have been given safely over 5–6 minutes.[19]
Continuous infusion	One paper noted a dose of 5 mg/kg/min.[20]

Levetiracetam

Other routes of administration	None reported.

Comments

Monitoring: Virtually no laboratory tests are altered.[2] Although abnormalities have been noted in hematologic parameters (e.g., decreases in RBC counts, hemoglobin, hematocrit, WBC counts and neutrophils) and serum transaminases (increased), the values remained within the normal range.[21,22] Benefit of therapeutic drug monitoring has not been established[2]; however, concentrations of 6–20 mg/L were noted in *adults* given doses of 1000–3000 mg/day.

Drug interactions: Levetiracetam is not a substrate for any CYP-isozyme, is not highly protein bound, and does not interfere with the metabolism of other anticonvulsants.[23] No clinically significant drug interactions have been reported.[2]

Levocarnitine

Brand names	Carnitor, generic
Medication error potential	Look-alike, sound-alike drug names. USP reports that Levocarnitine has been confused with levetiracetam, but patient harm did not occur.[1]
Contraindications and warnings	None known.
Infusion-related cautions	None known.
Dosage	**Hemodialysis:** 10–40 mg/kg/dose following dialysis.[2–4] Others support the use of considerably smaller doses of 2–5 mg/kg/dose following dialysis.[5–7] The clinical practice recommendations for anemia in chronic kidney disease in children state there is no firm evidence to support its use.[8] **Primary carnitine deficiency/metabolic disorders:** A loading dose of 50 mg/kg followed by 50–60 mg/kg/day divided q 3–6 hr or given by continuous IV infusion.[2,9] **PN supplementation in neonates/infants with little or no enteral intake:** 10–30 mg/kg/day.[10–18] **Valproate-associated hepatotoxicity** **Active hepatotoxicity/overdose:** 150–500 mg/kg/day, up to 3 g/day.[19,20] **Prophylaxis against valproate or other anticonvulsant-associated hepatotoxicity:** 15–100 mg/kg/day has been used in children with or without hyperammonemia.[20] Decreased ammonia levels, in those with hepatotoxicity, were seen after 9 days of treatment with 1000 mg/m^2/day divided in 2 equal doses.[21] **Other uses:** See Comments section.
Dosage adjustment in organ dysfunction	No dose adjustment recommended; however, carnitine is excreted renally and renal insufficiency may lead to the accumulation of potentially toxic metabolites.[2,8]
Maximum dosage	**PN supplementation:** 48 mg/kg/day has been given.[22] (See Comments section.) **Metabolic disorders:** 300 mg/kg/dose (age not specified).[2] **Valproate-induced hepatotoxicity:** 3 g/day.[19,20] **Valproic acid (VPA)/anticonvulsant therapy:** 100 mg/kg/day or 1000 mg/m^2/day.[20]
Additives	None reported.
Suitable diluents	NS, LR.[2]
Maximum concentration	1 g/5 mL (200 mg/mL).[2]

Levocarnitine

Preparation and delivery	**Preparation:** Mix with suitable diluents to concentrations of 0.5–8 mg/mL.[2] **Stability:** May be stored at room temperature for up to 24 hours in PVC bags.[2] **Compatibility:** May be added to PN solutions and infused over 24 hours or during a PN cycling schedule.[10,13,15–18] One study documented stability of carnitine via PN and TNA with Y-site administration of 20% fat emulsion at all study points (IV bag, distal to filter, after mixing with fat emulsion) for up to 24 hours at room temperature and up to 30 days when stored at 4°C to 5°C[23]; however, another study evaluated stability with carnitine in TNA and observed creaming.[24]
IV push	200 mg/mL over 2–3 minutes.[2]
Intermittent infusion	May give by intermittent infusion.[2,9]
Continuous infusion	May be given by continuous infusion.[2]
Other routes of administration	No information available to support administration by other routes.
Comments	**Significant adverse effects:** L-carnitine (oral and IV) can cause seizures in patients with and without a pre-existing seizure disorder.[2] Children and infants who received large doses and experienced seizures had other risk factors, including microcephaly, and metabolic acidosis.[11] Higher metabolic rate, greater nitrogen excretion, and lower weight gain has been reported following 48 mg/kg/day given via PN in 12 preterm neonates. **Miscellaneous:** IV carnitine has been beneficial in childhood cardiomyopathy.[25] Life-threatening lactic acidosis associated with reverse transcriptase inhibitors was corrected in an HIV-positive, 10-year-old patient with 12–50 mg/kg/day L-carnitine.[26] Neuroprotective therapy with L-carnitine (150 mg TID), pyridoxine (35 mg daily), and N-acetylcysteine (50 mg BID) was given to a 35-week gestation preterm infant with acute lymphoblastic leukemia who developed vincristine-associated neuropathy after the first phase of induction therapy (weight of 2.3 kg during induction therapy). Neuroprotective therapy was initiated at 46 days of age; neurologic recovery began at 57 days of age, and the infant had complete neurologic recovery by 5 months of age.[27]

Levothyroxine Sodium

Brand names

Synthroid, generic

Medication error potential

Look-alike, sound-alike drug names.

ISMP and USP report that levothyroxine has been confused with lamotrigine and Lanoxin.[1,2] The USP also reports that levothyroxine has been confused with amantadine, digoxin, leucovorin, Levaquin, levofloxacin, levonorgestrel, levorphanol, and liothyronine.[2]

USP reports that Synthroid has been confused with Symmetrel and thyroid.[2]

Contraindications and warnings

U.S. boxed warning: Should not be used for weight loss or the treatment of obesity. Large doses of levothyroxine needed for weight loss in euthyroid patients produce serious and life-threatening toxicity, particularly when given in combination with sympathomimetic agents.[3]

Other warnings: Recommend cautious initiation of therapy in patients with cardiovascular disease, endocrine disorders, and thyrotoxicosis.[3]

Infusion-related cautions

Large, sudden doses of IV levothyroxine may have cardiovascular risks.[3]

Dosage

Congenital or acquired hypothyroidism

Age	Starting IV Dose is Approximately 50% to 75% of the Oral Doses[4] Listed Below
0–3 mo	10–15 mcg/kg/day[4–6]
3–6 mo	8–10 mcg/kg/day[4]
6–12 mo	5–8 mcg/kg/day[5]
1–3 yr	4–6 mcg/kg/day[5]
3–10 yr	3–5 mcg/kg/day[5]
>10 yr	2–4 mcg/kg/day[5]
Growth and puberty complete	1.6–1.7 mcg/kg/day[4]

The AAP recommends an initial oral dosage of 10–15 mcg/kg/day for infants with hypothyroidism.[7] IV dose should be 50% to 75% of oral doses.[4]

The goal of therapy is to normalize T4 within 2 weeks and TSH within 1 month.[7] Neonates and infants with very low or undetectable serum T4 concentrations (<5 mcg/dL) should be started at the higher end of the dosage range.[4] Patients with evidence of cardiac disease or long-standing or severe hypothyroidism should receive a lower starting dose.[3] Adjust dosage based on clinical response and serum free T4 and TSH.[3,7]

Premature infants <30 weeks gestational age who received 5 mcg/kg/day were reported to be at increased risk of refractory hypotension.[8]

Dosage adjustment in organ dysfunction

No information available.

Maximum dosage

Not established. In *adults* with myxedema coma or stupor, without concomitant severe heart disease, may give doses of 200–500 mcg.[3]

Additives

10 mg mannitol per vial.[3,9]

Levothyroxine Sodium

Suitable diluents	Use only NS for reconstitution.[3,9]
Maximum concentration	100 mcg/mL[3]
Preparation and delivery	Reconstitute with NS only. Use immediately.[3]
IV push	40–100 mcg/mL in NS.[3]
Intermittent infusion	No information available to support administration by this method. Should not be mixed with IV infusion solutions.[3,9]
Continuous infusion	No information available to support administration by this method. Should not be mixed with IV infusion solutions.[3,9]
Other routes of administration	May be administered by IM injection[3,9]; however, because absorption is variable following IM administration, IV is preferred.[4]
Comments	**Adverse effects:** Pseudotumor cerebri has been reported to follow levothyroxine therapy in both *adults* and infants and children.[10] **Drug interactions:** Because levothyroxine is associated with numerous drug interactions, consult appropriate resources for dosing recommendations before combining any drug with levothyroxine. **Other:** The aim of therapy is to ensure normal growth and development.[7] Early, high-dose levothyroxine therapy has been shown to eliminate the negative impact that congenital hypothyroidism has on IQ and CNS development.[7,11,12]

Lidocaine HCl

Brand names	Xylocaine
Medication error potential	High-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. Confusion with bupivacaine and linezolid has been reported.[2]
Contraindications and warnings	**Contraindications:** In patients with a known history of hypersensitivity to local anesthetics of the amide type.[3] It should not be used in patients with Stokes-Adams syndrome, Wolff-Parkinson-White syndrome, or with severe degrees of sinoatrial, atrioventricular, or intraventricular block.[3] **Warnings:** Emergency resuscitative equipment and drugs should be immediately available to manage adverse reactions involving cardiovascular, respiratory, or CNS systems.[3]
Infusion-related cautions	Bronchospasm has been reported.[3] (See Rare Adverse Effects in the Comments section.) Local thrombophlebitis may occur with prolonged infusions.[3] Lidocaine hydrochloride products containing preservatives should not be given intravenously.[4]
Dosage	**Anesthesia, local injectable:** 4.5 mg/kg (maximum 300 mg). Dose varies based on procedure, vascularity of tissue, degree and duration of anesthesia required, and physical condition of patient. **Arrhythmias:** Use for pulseless ventricular tachycardia of fibrillation that is unresponsive to defibrillation, CPR, and epinephrine.[5] Lidocaine solutions that contain epinephrine must *not* be used to treat arrhythmias. (See Other Routes of Administration section for information related to ET and IO administration in those without IV access.) **Initial:** 0.5–1 mg/kg (maximum single dose 100 mg) q 5–10 min until desired effect or maximum total dose of 3–5 mg/kg.[5–7] Decrease loading dose by 50% in patients with reduced hepatic function or decreased hepatic blood flow (e.g., severe congestive heart failure or postcardiac surgery). **Maintenance:** 0.5–3 mg/kg/hr (10–50 mcg/kg/min).[5–7] If more than 15 minutes has lapsed between initial dose and start of infusion, give 0.5–1 mg/kg.[7] Smaller doses may be required in neonates with shock or patients with reduced hepatic function, decreased hepatic blood flow, and severe congestive heart failure. **Epilepsy (refractory status):** Initial dose of 1–3 mg/kg over 2 minutes.[8–17] If seizures do not stop in 2 minutes, give an additional dose of 0.5 mg/kg.[7] A continuous infusion of 2–6 mg/kg/hr effectively controlled severe intractable seizures in neonates,[10,11,16] infants,[12,13,17] and children.[14,17] A dose of 1.5–3.5 mg/kg/hr has been used in *adults*.[15] **Intracranial pressure (acute increases due to procedures):** 1–1.5 mg/kg given 30 seconds prior to intubation or ET suctioning to reduce airway reflexes.[5,18,19] **Pain associated with anti-GD2 antibody therapy:** A loading dose of 2 mg/kg infused over 30 minutes before antibody therapy, followed by a continuous infusion of 1 mg/kg/hr.[20] The infusion should be discontinued 2 hours after antibody therapy is stopped.
Dosage adjustment in organ dysfunction	Doses should not exceed 20 mcg/kg/min in patients with shock, congestive heart failure, liver failure, or decreased liver blood flow.[3,21,22] No adjustment in renal dysfunction.[3,23]

Lidocaine HCl

Maximum dosage	1 mg/kg (maximum single dose 100 mg) until desired effect or maximum total dose of 5 mg/kg[5–7] or <300 mg in 1 hour.[3] Administration of ≤88 mcg/kg/min (50 mg/min) by continuous infusion has been proposed.[24] Dosage should be titrated using serum concentration monitoring. (See Monitoring in the Comments section.)
Additives	Some multidose vials may contain sulfites and methylparabens.[4] (See Appendix C for specific information about sulfite hypersensitivity and paraben potential for toxicity.)
Suitable diluents	D5W, LR, NS, ½NS, D5-LR, D5¼NS, and D5½NS.[4]
Maximum concentration	20 mg/mL for IV push[4,7] and 8 mg/mL for infusion in fluid-restricted patients.[4]
Preparation and delivery	**Preparation:** Products containing 40, 100, or 200 mg/mL must be diluted before IV administration.[3,4] Usually 1 or 2 g of lidocaine hydrochloride is added to 1 L of D5W to form a solution of 1 or 2 mg/mL (0.1% or 0.2%), respectively.[3,4] **Stability:** Do not use if solution is discolored or cloudy.[3] **Compatibility:** See Appendix D for PN compatibility information.[25]
IV push	Generally over 2–3 minutes, not to exceed 0.7 mg/kg/min or 50 mg/min, whichever is less[3]; however, it has been given more rapidly in situations of ventricular tachycardia of fibrillation that is unresponsive to defibrillation, CPR, and epinephrine.
Intermittent infusion	Not recommended due to short half-life.[3]
Continuous infusion	Usually 1–2 mg/mL; however, 8 mg/mL in D5W has been used in fluid-restricted patients.[3]
Other routes of administration	Generally not given via other methods. Can be given IM into the deltoid muscle provided bradycardia is not present[3]; however, a formulation specific for IM delivery is no longer available in the United States. For ET administration, give 2–3 mg/kg/dose followed by a 5 mL flush of NS and five assisted manual ventilations.[5,7] For IO administration, give 1 mg/kg.[26]
Comments	**Rare adverse effects:** Transient mydriasis has been reported in a neonate treated with lidocaine for seizures.[26] Transient bronchospasm was noted in a 17-month-old with mild intermittent asthma.[27] **Monitoring:** Because large variability exists in patient response to initial and maintenance doses, individualize dosage based on serum concentration and clinical response. Reference range: 1.5–5 mg/L for antiarrhythmic effect.[3] Potentially toxic at serum concentrations above 6 mg/L and toxic above 9 mg/L.[28] The reference range for the management of status epilepticus has not been established. Monitor for bradycardia and hypotension. Widening of the QRS interval by >0.02 seconds prolongation of the PR interval, significant ventricular slowing, or the appearance or aggravation of arrhythmias suggests toxicity.[3] Excessive serum concentrations may also produce CNS symptoms (e.g., drowsiness, nausea, vomiting, disorientation, seizures, and muscle twitching).[3] **Drug interactions:** Should be used with caution in patients with digitalis toxicity accompanied by atrioventricular block.[3] Beta-blocking agents and cimetidine may reduce hepatic blood flow and decrease lidocaine clearance, which increases serum lidocaine concentrations to cause an increased incidence of adverse reactions. Consult appropriate resources for dosing recommendations before combining any drug with lidocaine.

Linezolid

Brand names

Zyvox

Medication error potential

USP reports confusion with lidocaine and lisinopril.[1] Confusion also reported between Zyvox and Avelox, Vioxx, Zithromax, Zosyn, Zovirax, and Zyflo.[1] The ISMP also reports confusion with Vioxx and Zovirax.[2]

Contraindications and warnings

Contraindications: In those with a known hypersensitivity reaction to linezolid or its components.[3]

Linezolid should not be used within 2 weeks of or in combination with a monoamine oxidase inhibitor.[3]

Serotonin syndrome could occur in patients receiving concurrent serotonergic agent (e.g., selective serotonin reuptake inhibitor [SSRI]).[3] Linezolid should not be administered to patients with Carcinoid syndrome or to those currently taking SSRIs, tricyclic antidepressants, buspirone, meperidine, or serotonin (5-HT1) receptor agonists.[3] (See Rare Adverse Effects in the Comments section.)

Unless patients are monitored for potential increases in blood pressure, linezolid should not be given to those with uncontrolled hypertension, thyrotoxicosis, pheochromocytoma, and/or patients with medicines that are direct or indirect acting sympathomimetics, vasopressive agents or dopaminergic agents.[3]

Warnings: Transient myelosuppression has been reported, especially when therapy lasts >2 weeks. CBC should be monitored more closely if (1) there is a known history of myelosuppression; (2) other bone marrow suppressing drugs are given; or (3) used in those with chronic infection who have received previous concomitant antibiotics.[3]

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[3] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[3]

Infusion-related cautions

If a decision is made to give this medication to a patient with known linezolid hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.

Dosage

Neonates

<table>
<tr><th>PNA</th><th>≤1200 g</th><th>1200–2000 g</th><th>≥2000 g</th></tr>
<tr><td><7 days</td><td rowspan="2">20–30 mg/kg/day divided q 8–12 hr[4–6]</td><td>20–30 mg/kg/day divided q 8–12 hr[4,6]</td><td>20–30 mg/kg/day divided q 8–12 hr[4–6]</td></tr>
<tr><td>≥7 days</td><td>30 mg/kg/day divided q 8 hr[3–8]</td><td>30 mg/kg/day divided q 8 hr[3–8]</td></tr>
</table>

*Until 4 weeks of age.

Infants and children (<12 yr): 30 mg/kg/day divided q 8 hr.[3,4,9–11]

Adolescents (≥12 yr): 20 mg/kg/day divided q 12 hr (up to 1200 mg/day divided q 12 hr.[3,4,12]

The manufacturer does not recommend the use of linezolid for empiric treatment of pediatric CNS infections.[3] Limited data, as *adult* and pediatric case reports, suggest that linezolid may be used to treat gram-positive CNS infections that failed to respond to other treatment.[13–16]

Dosage *(cont.)*	**Bacterial endocarditis (treatment):** Treatment of *E. faecium* endocarditis of native or prosthetic valve that is resistant to penicillin, aminoglycoside, and vancomycin: 30 mg/kg/day divided q 8 hr (not to exceed normal dosing of *adults*) for ≥8 weeks.[17] 45 mg/kg/day divided q 8 hr was reported in an infant with *E. faecium* endocarditis.[18] Linezolid has been used for methicillin-resistant *Staphylococcus aureus* endocarditis in an extremely low birth weight neonate.[19] **Central line infections:** 2 mg/mL plus 100 units of heparin as an 8-hour catheter lock.[20] May be used in combination with 30 mg/kg/day divided q 8 hr of systematic linezolid. Another method instilled 3 mL of a linezolid solution (2 g/L) into the lumen of the catheter for 16 hours without the use of heparin.[21]
Dosage adjustment in organ dysfunction	No adjustment in renal impairment.[3,22] Although metabolites may accumulate in renal insufficiency, the clinical significance is unknown.[3] No adjustment in mild-to-moderate hepatic impairment; caution should be used in severe hepatic impairment.[3]
Maximum dosage	45 mg/kg/day divided q 8 hr was given to a 7-week-old infant.[18] 1200 mg/day if >12 years of age.[3,4]
Additives	100 mL contains 1.7 mEq sodium, 200 mL contain 3.3 mEq of sodium, and 300 mL contains 5 mEq of sodium.[3,23]
Suitable diluents	Compatible with D5W, NS, and LR.[3] May be given undiluted.[23]
Maximum concentration	2 mg/mL (commercially available).[3,23]
Preparation and delivery	**Stability:** Do not freeze. The solution is a yellow color that can intensify with no affect on potency.[23] **Compatibility:** See Appendix D for PN compatibility information.[24]
IV push	Not recommended.[3]
Intermittent infusion	2 mg/mL over 30–120 minutes.[3,23]
Continuous infusion	Use of 1200 mg/day or 30 mg/kg/day by continuous infusion has been reported.[25,26]
Other routes of administration	None.
Comments	**Rare adverse events:** Lactic acidosis has been reported in some patients that experience repeat nausea and vomiting.[3,27] Death has been reported; however, most patients' serum lactate levels return to normal after discontinuation of linezolid.[28,29] Nonspecific clinical symptoms make it difficult to detect; therefore, serum bicarbonate or lactate levels should be monitored.[28,29] Peripheral and optic neuropathy has occurred with treatment >28 days; however, it can manifest within days to months. Linezolid should be discontinued if neuropathy is attributed to linezolid. Recovery is variable.[28] Peripheral and optic neuropathy has been reported in children.[30,31]

Linezolid

Comments *(cont.)*

Serotonin syndrome has been reported in patients given concurrent serotonergic agents.[3,32,33] A 4-year-old burn victim who received linezolid and fluoxetine became agitated and developed myoclonic movement in limbs.[34] Symptoms resolved following discontinuation of linezolid.

Brownish tooth and tongue discoloration has been reported in pediatric patients receiving IV linezolid.[35] The discoloration is reversible with discontinuation of linezolid and with manual removal by a dentist.[35,36]

Convulsions have been reported in pediatric patients receiving linezolid.[10] One report described a patient with known epilepsy who experienced an increased frequency and worsened control of seizures while on IV linezolid therapy that occurred again with re-challenge.[37]

In a 2-year-old boy receiving linezolid for treatment of infective endocarditis, progressive fatigue and anemia developed 2 weeks post-linezolid initiation. Four days after discontinuation of linezolid hemoglobin (Hb), hematocrit (Hct), and reticulocyte increased.[38]

Monitoring: Serum bicarbonate, serum transaminases, CBC and platelet, blood pressure, and signs or symptoms of serotonin syndrome (e.g., hyperreflexia, clonus, hyperthermia, etc.). Although transient thrombocytopenia may occur,[3,39] one study found no significant difference in the platelet count for linezolid (n=215) versus vancomycin (n=101) treated pediatric patients.[40]

Drug interactions: Consult appropriate resources for dosing recommendations before combining any drug with linezolid.

LORazepam

Brand names	Ativan
Medication error potential	High-alert medication associated an increased risk of causing significant patient harm if an error occurs.[1] Look-alike, sound-alike drug name. Confusion with alprazolam, clonazepam, diazepam, loperamide, loratadine, midazolam, oxazepam, temazepam and zolpidem have been reported. Confusion has also been noted between Ativan and alprazolam, Ambien, Antivert, Artane, Atarax, and clonazepam. Confusion with alprazolam has resulted in patient harm.[2] ISMP recommends the following tall man letters (not FDA approved): LORazepam.[3]
Contraindications and warnings	**Contraindications:** Should not be used in patients with (1) a known sensitivity to benzodiazepines or its vehicles (polyethylene glycol, propylene glycol, and benzyl alcohol); (2) acute narrow-angle glaucoma; (3) sleep apnea syndrome; and (4) severe respiratory insufficiency (except in those patients requiring relief of anxiety and/or diminished recall of events while being mechanically ventilated).[4] (See Infusion-Related Cautions section.)
Infusion-related cautions	Respiratory depression may occur; hence, artificial ventilation equipment should be available. Inadvertent intra-arterial injection can cause vasospasm that may produce gangrene and subsequent amputation.[4] If a patient complains of pain during injection, the infusion should be stopped, and the IV site should be inspected.
Dosage	Flumazenil should be readily available for reversal. (See Other in the Comments section and see Flumazenil monograph.) **Adjunct to antiemetic therapy:** Single doses of 0.01 mg/kg have been used pre-operatively for nausea associated with strabismus surgery[5]; however, single doses of at least 0.04 mg/kg (maximum 3 mg/dose) were required for emesis associated with chemotherapy.[6,7] Multiple doses of 0.04–0.08 mg/kg (maximum 2 mg/dose) may be given q 6 hr PRN.[7] **Adjunct for procedural sedation[8,9]:** Many consider midazolam the benzodiazepine of choice for procedural sedation.[10–13] (See Midazolam monograph.) 0.05 mg/kg (0.01–0.1 mg/kg) q 4–8 hr[9] not to exceed 2 mg/dose.[4,8] For premedication therapy, give first *IV* dose 15–20 minutes before procedure and first *IM* dose 2 hours before procedure. **Sedation with mechanical ventilation:** Use lowest effective dose. 0.025–0.05 mg/kg (maximum initial dose of 2 mg) given as intermittent infusion q 2–4 hr or by continuous infusion, at a rate of 0.025 mg/kg/hr (up to 2 mg/hr).[13] (See Additives and Comments sections if given by continuous infusion.) **Seizures** **Prophylaxis (busulfan-associated seizures)[14–16]:** 0.02–0.05 mg/kg (up to 2 mg/dose) given 30 minutes before each dose of busulfan.[15] Give 0.02 mg/kg if <2-years-old over 30 minutes. Continue every 6 hours for 4 additional doses after the last dose of busulfan.[15] 0.1 mg/kg/day (up to 2 mg/day) has been given by continuous infusion.[14] The infusion was started 12 hours before busulfan and was discontinued 24 hours after the last dose of busulfan.[14] Duration of infusion was 5.5 days.[14] **Treatment** **Neonates:** In a recent survey of neonatologist, 82% (n = 480) of neonates would give phenobarbital as the preferred anticonvulsant.[17] 0.05–0.1 mg/kg.[18–21] If seizures continue after 10–15 minutes, repeat 0.05 mg/kg; if no response after 10–15 minutes, repeat 0.05 mg/kg to a maximum of 0.15 mg/kg.[19] (See Pharmacokinetic Considerations and Pharmacodynamic Considerations in the Comments section and Appendix C.)

Dosage *(cont.)*	**Infants and children:** 0.1 mg/kg[18–25] up to 4 mg/dose.[23] If seizures continue after 10–15 minutes, repeat 0.05 mg/kg; if no response after 10–15 minutes, repeat 0.05 mg/kg.[22–24]
Dosage adjustment in organ dysfunction	No adjustment in renal dysfunction due to LORazepam.[4,26] Patients receiving large doses for a prolonged time my accumulate propylene glycol and experience toxicity.[27,28] (See Comments section and Appendix C.) Not metabolized by cytochrome oxidation, thus liver disease should not have an effect on metabolic clearance[4]; however, it may worsen hepatic encephalopathy.[29] Use cautiously in patients with combined renal and hepatic dysfunction.[4]
Maximum dosage	4 mg/dose.[11,23] Doses as large as 0.4 mg/kg have been safely administered.[5,30] A 14-year-old with refractory seizures who had been on chronic LORazepam was given 0.25 mg/kg/dose to a cumulative dose of 186 mg (4.3 mg/kg) over 24 hours.[31] Patients on benzodiazepines prior to admission may require larger doses for control.
Additives	Contains benzyl alcohol 2% and 40% propylene glycol.[32] (See Appendix C for specific information about benzyl alcohol and propylene glycol potential for toxicity.)
Suitable diluents	D5W, NS, SW.[4,32] Although the manufacturer recommends diluting the commercially available solution 1:1 in D5W, NS, or SW,[4] undiluted solutions of 2[25] and 4 mg/mL[23] have been given.
Maximum concentration	Although 4 mg/mL[23] has been given, the manufacturer recommends dilution to ≤1 mg/mL.[4]
Preparation and delivery	**Stability:** Store in refrigerator.[4,32] **Delivery system issues:** Larger doses may be required in patients on extracorporeal membrane oxygenation since 50% of a dose may be extracted by the PVC tubing and the membrane oxygenator during bypass.[33] **Compatibility:** See Appendix D for PN compatibility information. **Photosensitivity:** The commercial product should be protected from light until ready to use.[4]
IV push	Not to exceed 2 mg/min[4,25] or 0.05 mg/kg over 2–5 minutes.[18]
Intermittent infusion	Not administered by this method.
Continuous infusion	0.2 mg/mL has been administered in *adults*[34–38]; however, little information is available in pediatric patients.[13,14] Midazolam is preferred when a benzodiazepine is given by continuous infusion due to propylene glycol accumulation. (See Comments section.)
Other routes of administration	Midazolam is the benzodiazepine of choice for IM and prehospital administration.[39] (See Midazolam monograph.) Although undiluted LORazepam can be given deep into a muscle, it may cause pain at the injection site, a sensation of burning, or observed redness.[4]

LORazepam

Comments

Rare adverse effects: Continuous infusion of medications containing propylene glycol has been known to cause hyperosmolality, increased anion gap and osmolar gap metabolic acidosis (due to lactic acidosis), acute kidney injury, and sepsis-like syndrome.[27,28,40–44] This most frequently occurs in patients with renal dysfunction, who were receiving prolonged infusions of drugs that contain propylene glycol.[27,28] For this reason, midazolam is preferred when a continuous infusion of a benzodiazepine is required. (See Comments section and Midazolam monograph.)

Paradoxical reactions (i.e., anxiety, excitation, hostility, aggression, rage, etc.) may occur in children and have been reported in 10% to 30% of those <8 years of age.[4] Brief tonic-clonic seizures have occurred in patients with atypical absence (petit mal) status epileptics who receive a benzodiazepine.[4] Seizure activity and myoclonus have also been reported following administration, especially in very low birth weight neonates.[4,45,46] The movements began a few minutes after a bolus injection and continued for several hours.[40,45,46]

Drug interactions: Consult appropriate resources for dosing recommendations before combining any drug with LORazepam.

Pharmacokinetic considerations: Mean total clearance normalized to bodyweight was reduced by 80% in neonates (≥37 weeks gestational age) compared to normal *adults.*[4] Terminal half-life was prolonged threefold, and volume of distribution was decreased by 40% in neonates with asphyxia neonatorum compared to normal *adults.*[4]

Pharmacodynamic considerations: Use in neonates is controversial because benzodiazepines may decrease blood pressure and cerebral blood flow velocity.[47] Some recommend the initial dose should be reduced by 50% in infants <2 months of age[13]; regardless, LORazepam should be used cautiously in neonates.

Other: Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for complete or partial reversal of benzodiazepine toxicity.[48,49] (See Flumazenil monograph.)

Rebound or withdrawal symptoms may occur following abrupt discontinuation or large decreases in dose.[4] Use caution when reducing dose or withdrawing therapy; decrease slowly and monitor for withdrawal symptoms.

Lymphocyte Immune Globulin–Antithymocyte Globulin (Equine)

Brand names	Atgam
Medication error potential	None noted.
Contraindications and warnings	**U.S. boxed warning:** Only physicians experienced in immunosuppressive therapy for renal transplant or aplastic anemia patients should use lymphocyte immune globulin–antithymocyte globulin (equine).[1] Patients receiving lymphocyte immune globulin–antithymocyte globulin (equine) should be treated in facilities equipped and staffed with adequate laboratory and supportive medical resources.[1] **Contraindications:** Patients who have a severe systemic reaction including a generalized rash, tachycardia, dyspnea, hypotension, or anaphylaxis to a previous Atgam infusion or any other equine gamma globulin product.[1]
Infusion-related cautions	The manufacturer recommends that patients be tested with an intradermal injection of 0.1 mL of 1:1000 dilution and a contralateral saline control. Sites should be observed every 15 minutes for 1 hour. A wheal or erythema ≥10 mm or marked local swelling should be considered a positive test. In the event of a positive test, alternative therapies should be considered and the risk benefit ratio weighed. A negative test dose does not preclude the possibility of an anaphylactic reaction.[1] Chills, fever, itching, and erythema can be controlled with antipyretics, antihistamines or corticosteroids.[1] Many centers have developed premedication protocols to minimize these reactions.
Dosage	**Transplant** **Renal:** 5–25 mg/kg/day for 5–14 days[1–4] followed by 10–20 mg/kg as a single dose every other day for ≤2 weeks after transplant.[5] Duration of therapy may be longer in cadaveric allograft recipients.[3] 15 mg/kg/day has been used for rejection of renal transplants.[6] **Bone marrow:** 30–40 mg/kg/day over 12 hours for 3–4 days prior to transplantation[7–10] and/or 20 mg/kg every other day for 6–8 doses beginning the day before or after transplantation.[9,11] **Lung and/or cardiac transplant:** 15–25 mg/kg/day for 3–7 days after transplant.[12,13] **Cord blood transplant in infant leukemia:** 30 mg/kg/day for 3 days before transplantation.[14] **Aplastic anemia:** 15 mg/kg/day for 5–10 days,[15,16] 10 mg/kg/day for 5 days,[17] or 40 mg/kg/day over 4 hours for 4 days.[18–22] **Graft-versus-host disease:** 30 mg/kg/day q other day for 6 doses[23] or 15 mg/kg over 3 hours BID for 5 days for steroid-resistant disease.[24]
Dosage adjustment in organ dysfunction	None noted. (See Comments section.)
Maximum dosage	Not established. The largest reported dose was 7 g in an *adult*.[1]

Lymphocyte Immune Globulin–Antithymocyte Globulin (Equine)

Additives	Contains 0.3 M glycine.[1]
Suitable diluents	D5¼NS, D5½NS, or NS.[1]
Maximum concentration	4 mg/mL.[1]
Preparation and delivery	Store refrigerated. Add Atgam to an inverted container of the sterile diluent to avoid contact with the air; swirl or rotate to mix. Do not shake. The diluted infusate should be at room temperature prior to infusion.[1] **Compatibility:** Addition to dextrose injection is not recommended because low-salt concentrations can cause precipitation.[1]
IV push	Not indicated.[1]
Intermittent infusion	Over ≥4 hours into a high-flow vein.[1] A 0.2–1 micron in-line filter should be used.[1] Resuscitative equipment should be at the bedside during infusion.[1]
Continuous infusion	Not indicated.
Other routes of administration	Not indicated.
Comments	**Adverse effects:** Phlebitis occurred in 46% of children given the drug through a peripheral vein.[6] One study, including six pediatric patients from 7–16 years of age, reported that infusion of Atgam (15 mg/kg) plus 1000 units heparin and 20 mg Solu-Cortef per 250–500 mL of ½NS over 4–6 hours was associated with a peripheral IV site complication rate of 3.2%.[25] Hence, the study concluded that Atgam could be safely administered via a peripheral vein. Thrombocytopenia,[6] neutropenia,[26] and serum sickness[1,26] have occurred. Treatment of serum sickness with corticosteroids has generally resulted in resolution of symptoms.[1] Treatment should be discontinued if severe and unremitting thrombocytopenia and leukopenia occurs.[1] This product is made using both human and equine blood components; thus, there is a risk of the transmission of infectious agents, including viruses and the prion that causes Creutzfeldt-Jakob disease.[1] **Monitoring:** Monitoring for bacterial and viral infections during therapy is important.[1,12] Antimicrobial prophylaxis may be included as a part of the treatment regimen.[3,12] Antibiotics can be discontinued if fever persists <48 hours and cultures are negative.[27]

Lymphocyte Immune Globulin–Antithymocyte Globulin (Rabbit)

Brand names	Thymoglobulin
Medication error potential	None noted.
Contraindications and warnings	**U.S. boxed warning:** Only physicians experienced in immunosuppressive therapy for renal transplant patients should use lymphocyte immune globulin-antithymocyte globulin (rabbit).[1] Serious immune-mediated reactions such as anaphylaxis may occur.[1] **Contraindications:** Patients who have a history of allergy or anaphylaxis to rabbit proteins or product excipients. Patients who have active infections that contraindicate additional immunosuppression.[1]
Infusion-related cautions	Fever, chills, dyspnea, hypotension or hypertension, rash, nausea/vomiting may occur during the infusion. Premedication with corticosteroids, acetaminophen, and an antihistamine or decreasing the infusion rate may lessen the incidence and duration of the reaction.[1] Infusion site reactions include pain, swelling, and erythema.[1]
Dosage	**Transplant** **Renal:** 1.5 mg/kg intra-operatively followed by 1.5 mg/kg/day for 4–14 days[1,2] or 1.5–2 mg/kg/day for up to 15 days during induction therapy.[3,4] Others reported administering 0.5–2.5 mg/kg/day for up to 14 doses.[5] More recently, 5 mg/kg was given q 24 hr for 2 doses followed by 2.5 mg/kg/day for 6–10 doses.[6] **Liver and/or intestinal:** 5 mg/kg divided in 2 doses and infused just prior to and soon after transplantation.[7–10] **Bone marrow:** 2–2.5 mg/kg/day infused over 1 hour for 3–5 days before transplantation (cumulative dose up to 10 mg/kg).[11,12] **Cardiac:** 1–2 mg/kg/day or every other day infused over 12 hours as induction therapy for a total of 5 doses.[13] 1–2.5 mg/kg/day for 1–7 days as induction therapy has also been used.[14] **Aplastic anemia:** 2.5–3.5 mg/kg/day infused over 6–8 hours for 5 days either as initial treatment or following relapse.[15–18] A recent study found horse lymphocyte immune globulin to be superior to rabbit lymphocyte immune globulin at 3.5 mg/kg/day for 5 days.[19]
Dosage adjustment in organ dysfunction	None noted.
Maximum dosage	Not established.[1] One study administered up to 150 mg/day.[5]
Additives	Contains 50 mg of glycine, 50 mg of mannitol, 10 mg of sodium chloride, and no preservatives.[1,20]
Suitable diluents	NS, D5W.[1,20]
Maximum concentration	0.5 mg/mL.[1,20]

Lymphocyte Immune Globulin–Antithymocyte Globulin (Rabbit)

Preparation and delivery	**Reconstitution:** The lyophilized powder should reach room temperature prior to reconstitution with SW.[1,20] **Photosensitivity:** Protect from light during storage.[1,20]
IV push	Not indicated.
Intermittent infusion	Over ≥6 hours into a high-flow vein for the first dose.[1] Subsequent doses can be infused over 4 hours according to patient tolerance. A 0.22-micron in-line filter should be used.[1]
Continuous infusion	Not indicated.
Other routes of administration	Not indicated.
Comments	**Adverse effects:** If the WBC count is ≥2000–3000/mm^3 or if platelet levels are ≥50,000–75,000/mm^3, the dose should be decreased by half. The drug should be stopped if the WBC count is <2000/mm^3 or platelet levels are <50,000/mm^3.[1] Patients are at an increased risk for infectious complications. The use of anti-infective prophylaxis is recommended.[1] **Monitoring:** Measurement of T-cell counts (absolute and/or subsets) helps assess T-cell depletion.[1] The WBC count and platelet levels should be monitored during therapy.[1]

Magnesium Sulfate

Brand names	Various manufacturers; concentrations of 50%, 8%, 4%, 2%, and 1% are available
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that magnesium sulfate has been confused with morphine sulfate. No harm resulted.[2]
Contraindications and warnings	Contraindicated in patients with heart block or with myocardial damage.[3]
Infusion-related cautions	Magnesium is available in several different salt forms, and magnesium sulfate is available in multiple concentrations. Choose products carefully.
Dosage	1 g magnesium sulfate = 8.12 mEq magnesium = 98.6 mg elemental magnesium.[4] **Hypomagnesemia** **Neonates:** 25–50 mg magnesium sulfate/kg q 8–12 hr for 2 or 3 doses.[4–6] (See Comments section.) **Infants and children:** 25–50 mg magnesium sulfate/kg (maximum 2 g/dose) q 6 hr for 3 or 4 doses.[4] One 9-year-old, 19-kg child receiving a 21-day course of tobramycin developed tetany, hypomagnesemia (serum magnesium 1 mg/dL), and hypocalcemia and was treated with 950 mg magnesium sulfate and 2 g calcium gluconate and had symptom improvement within hours.[7] **PALS (torsades de pointes, resuscitation with hypomagnesemia):** 25–50 mg magnesium sulfate/kg up to a maximum of 2 g. A more rapid infusion rate (bolus over several minutes) may be needed in pulseless torsades de pointes.[8,9] **Asthma:** 25–75 mg magnesium sulfate/kg up to a maximum of 2 g infused over 15–30 minutes.[8,10–18] **Epilepsy:** 20–100 mg magnesium sulfate/kg q 4–6 hr.[4] Doses up to 200 mg/kg have been used. Daily magnesium sulfate 250 mg/kg for 3 weeks as an adjunct to adrenocorticotropic hormone was studied in 19 patients with infantile spasms.[19] **Following cardiopulmonary bypass (CPB):** 25–50 mg magnesium sulfate/kg up to a maximum up 2 g.[20,21] In one study, the development of arrhythmias was compared in those given 30 mg magnesium sulfate/kg (n = 13) or saline control (n = 15) after CPB.[20] If serum magnesium concentration decreased to <1.6 mg/dL at any time during the ICU stay, 10 mg/kg was given. Junctional ectopic tachycardia occurred in 27% of the saline control group (n = 15) compared to none of the treatment group. **Perinatal/birth asphyxia in term newborns with hypoxic ischemic encephalopathy:** 250 mg magnesium sulfate/kg over 1 hour q 24 hr for 3 doses.[22] **Persistent pulmonary hypertension of the newborn (PPHN):** 200 mg magnesium sulfate/kg over 30 min as an initial dose[23–25] followed by an infusion of 20–50,[23] 20–100,[25] or 50–150[24] mg magnesium sulfate/kg/hr. Seven of nine infants who received 200 mg magnesium sulfate/kg followed by 20–50 mg/kg/hr for up to 8 hours survived.[23] Predicted mortality in these patients was 100%. These high-dose magnesium sulfate regimens are studied primarily in developing countries where advanced treatments for PPHN such as inhaled nitric oxide, extracorporeal membrane oxygenation, or high-frequency oscillatory ventilation are not available.[24,25]

Magnesium Sulfate

Dosage adjustment in organ dysfunction	Use with caution in severe renal insufficiency.[3] The manufacturer recommends that in severe renal insufficiency doses not exceed 20 g in 48 hours and serum magnesium concentration be obtained often.
Maximum dosage	In children with hypomagnesemia, 2 g/dose.[4,9] Up to 40 g/day has been used in *adults* with pre-eclampsia to treat or prevent seizures.[3]
Additives	Contains contaminant aluminum.[3]
Suitable diluents	D5W, NS, LR.[3,26]
Maximum concentration	200 mg/mL or 1.6 mEq/mL (20%) for IV infusion in children or *adults*.[3] 20% for IM administration in infants and children, 50% for IM administration in *adults*.[3,4]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.
IV push	Infrequently used due to the potential for increased adverse effects.[3] (See Comments section.)
Intermittent infusion	Usually over 10–30 minutes for acute/emergent hypomagnesemia or asthma, or over 1–4 hours for magnesium replacement in infants and children.[4–6,11,13,15,17] ≤150 mg/min in *adults*.[3]
Continuous infusion	≤200 mg/mL concentration (20%) for continuous infusion.[3,26]
Other routes of administration	IM.[3]
Comments	**Monitoring:** Monitor for cardiac dysrhythmias, hypotension, respiratory depression, and CNS depression during intermittent infusion.[3,6] In neonates, infusion of 250 mg magnesium sulfate/kg over 10 minutes was associated with respiratory depression and infusion of 400 mg/kg over 10–30 minutes was associated with an unacceptable rate of hypotension.[27] **Drug interactions:** Drug interactions between magnesium and CNS depressants and neuromuscular blockers can occur.[3] Treatment of hypermagnesemia with calcium in patients receiving digoxin can result in heart block.[28]

Mannitol

Brand names	Osmitrol, generic
Medication error potential	None noted.
Contraindications and warnings	**Contraindications:** Patients with a known hypersensitivity to mannitol or its ingredients should not receive the medication. Well-established anuria due to severe renal disease, severe pulmonary congestion or frank pulmonary edema, active intracranial bleeding except during craniotomy, severe dehydration, and progressive renal dysfunction. If progressive heart failure or pulmonary congestion develops after starting mannitol the drug should be stopped.[1] **Warnings:** Excessive fluid and electrolyte losses can occur; serum electrolytes, especially sodium and potassium, should be monitored.[1]
Infusion-related cautions	Rapid administration can cause hypotension, hyperosmolality, and elevations in intracranial pressure (ICP).[2]
Dosage	**Acute renal failure (oliguria)** **Assessment of renal function:** The manufacturer recommends that patients with marked oliguria or suspected renal insufficiency be given a test dose before beginning IV mannitol therapy. 0.2 g/kg to a maximum of 12.5 g over 3–5 minutes to produce a urine output of ≥1 mL/kg/hr or 30–50 mL/hr in *adults* for 1–3 hours.[1,3] This may be repeated after 2 hours if the response is inadequate. **Treatment:** 0.25–2 g/kg/dose over 2–6 hours.[1,4,5] Should not be repeated if oliguria persists.[1] Mannitol is not recommended for the prevention of acute renal failure.[6] **Cerebral edema/elevated ICP:** Generally used short-term for diagnostic procedures or for prolonged therapy for elevation ICP.[7] 0.25–1 g/kg over 15 minutes.[2,3,8–12] The AAP recommends 0.25 g/kg given over 5–15 minutes repeated PRN and 0.5 g/kg given over 15 minutes for an acute increase in ICP.[2] There is little information on the repeated, regular use of mannitol over several days.[7] There is a lack of evidence to support or refute using mannitol in severe traumatic brain injury.[13] (See Comments section.) **Nephrotic syndrome:** Three children (ages 4, 7, and 9 years) with nephrotic syndrome and diuretic-resistant edema responded to furosemide (2 mg/kg) and 5 mL/kg/day of 20% mannitol infused over 1 hour for 5–7 days.[9]
Dosage adjustment in organ dysfunction	Mannitol should not be used in patients with severe renal disease and well-established anuria.[1]
Maximum dosage	2.5 g/kg has been used in *adults*.[8] However, there does not appear to be a therapeutic advantage to doses >1 g/kg.[8]
Additives	None reported.
Suitable diluents	D5W.[1]
Maximum concentration	25% solution.[1,14]

Mannitol

Preparation and delivery	**Stability:** Mannitol ≥15% solution may crystallize at lower temperatures.[14] To avoid crystal formation, store the solutions in a warming chamber or if crystals are present, warm the vial using a dry heat cabinet and vigorous shaking. Be sure the solution is at body temperature prior to infusion. Mannitol crystals in glass ampuls have been resolubilized, using a microwave, with no evidence of chemical decomposition; however, explosions of the ampuls have been reported.[14] Supersaturated mannitol solutions in PVC bags develop a heavy precipitate within minutes.[14] Heating the bag may temporarily dissolve the crystals; however, they may quickly reappear. **Delivery system issues:** Solutions containing ≥20% mannitol should be infused through an in-line filter.[1,14] **Compatibility:** See Appendix D for PN compatibility information.
IV push	3–5 minutes in oliguria.[1]
Intermittent infusion	Over 15–60 minutes for cerebral edema, elevated ICP, or preoperative in neurosurgery.[2,3,8–12]
Continuous infusion	Sixty patients from age 1–73 years were given a continuous infusion over 6–100 hours (total dose 2–20 g/kg).[8]
Other routes of administration	None reported.
Comments	**Adverse effects:** Mannitol increases the intravascular volume and can worsen hyponatremia. Use furosemide for increased ICP in patients with pre-existing cardiac disease because mannitol increases the intravascular volume and may exacerbate coronary heart failure and pulmonary edema.[15] A 16-year-old and a 28-year-old with increased ICP and normal renal function developed reversible acute renal failure after receiving 2 and 4 days of doses ranging from 50–900 g/day.[16] **Monitoring:** The resultant diuresis can lead to sodium and potassium losses. Electrolytes should be monitored.[1] Monitor serum osmolality during mannitol therapy for elevated ICP. **Osmolality:** 25% mannitol has an osmolarity of 1372 mOsmol/L.[1]

Meperidine HCl

Brand names	Demerol, generic
Medication error potential	High-alert medication that has an increased risk of causing significant patient harm if used in error.[1]
Contraindications and warnings	**Contraindications:** Those with hypersensitivity to meperidine and those on monoamine oxidase (MAO) inhibitors or who have recently received MAO inhibitors.[2] **Warnings:** Use with caution in those receiving other CNS depressants. Meperidine may elevate cerebrospinal fluid pressure and, if possible, an alternative agent should be used in patients with head injury.[2]
Infusion-related cautions	For IV infusion, the patient should be lying down.[2] Rapid injection may cause severe respiratory depression, apnea, hypotension, peripheral circulatory collapse, and cardiac arrest. For this use, the patient should be in a facility with appropriate supportive measures and a narcotic antagonist must be available. Anaphylaxis has been reported.[3]
Dosage	Because of the potential for adverse effects, meperidine has largely been replaced by other analgesics.[4–6] Doses should be titrated to desired analgesic effect. Demerol, Phenergan, Thorazine (DPT) cocktail has been used to sedate children.[7–10] However, safer and more effective agents are available,[7,9,11] and this combination is no longer recommended.[10] **Analgesia:** 0.5–2 mg/kg (usually IM or SC) q 3–4 hr PRN.[2,12–15] A loading dose of 0.3–1 mg/kg followed by continuous infusion, beginning at 0.3 mg/kg/hr and titrating to desired response up to 0.7 mg/kg/hr has been used in severe sickle cell pain crisis.[16] (See Comments section.) **Preoperative sedation:** 0.25–1.5 mg/kg (usually IM or SC) and ≤100 mg given 30–90 minutes prior to procedure.[11,17,18] 2 mg/kg and ≤100 mg has been used IV.[19]
Dosage adjustment in organ dysfunction	If CrCl is 10–50 mL/min/1.73 m^2, give 75% of the usual dose, and if CrCl is <10 mL/min/1.73 m^2, give 50% of the usual dose.[20] Avoid repeated or large doses in patients with renal impairment.[2] The dose or frequency of dosing should be decreased in hepatic disease.[2] Those with renal and hepatic disease are at risk for accumulation of normeperidine, an active metabolite.[21] (See Comments section.)
Maximum dosage	2 mg/kg[15,16,18,19] and ≤100 mg/dose.[2,19] A continuous infusion of 1.5 mg/kg/hr has been used in children with sickle-cell disease.[16] (See Comments section.)
Additives	Products may contain sodium metabisulfite and/or phenol and *m*-cresol as preservatives.[22] (See Appendix C for specific information about adverse effects.)
Suitable diluents	D–LR, D–R, D–S, D5W, D10W, LR, NS, or ½NS.[2,22]

Maximum concentration	10 mg/mL for IV injection. 1 mg/mL for IV infusion.[2]
Preparation and delivery	**Compatibility:** Meperidine is incompatible with heparin[22,23] and barbiturates.[2,22] To avoid precipitation with heparin, flush heparinized IV catheters with NS before and after meperidine injection.[22,23] See Appendix D for PN compatibility information.
IV push	Not indicated. Rapid injection increases risk for adverse reactions (e.g., respiratory depression, apnea, hypotension, cardiac arrest).[2] One group reported that five of 154 children undergoing endoscopy required supplemental oxygen for a short time after receiving 2 mg/kg infused over 1–2 minutes.[19]
Intermittent infusion	Over >5 minutes.[2]
Continuous infusion	May be used as continuous infusion.[2]
Other routes of administration	Usually given IM. SC can be used occasionally.[2,11,17] Local tissue irritation and induration are more common with SC administration.[2]
Comments	**Adverse effects:** The meperidine metabolite, normeperidine, may cause a variety of CNS effects including excitability, twitches, tremors, or seizures.[24,25] When pain management was inadequate with morphine, a 32-month-old febrile and hyponatremic boy with 90% body surface area (BSA) burns was changed to a meperidine infusion.[26] One hour after the dose had been gradually increased to 25 mg/kg/hr, he began having intermittent seizures and became comatose. The meperidine was stopped, phenobarbital was started, and the seizures stopped after 6 hours. While there were confounding factors, it was felt that the seizures were due to the large dose of meperidine. A 6-week-old infant received 2 IV doses of 1 mg/kg during rigid bronchoscopy and developed acute orofacial dyskinesias (e.g., tongue thrusting, pursing or puckering, facial grimacing) that were unresponsive to 0.1 mg/kg of naloxone.[27] This lasted about 36 hours; he had no residual effects. **Monitoring:** Vital signs, oxygen saturation, and pain relief.[15] **Pharmacokinetics:** The pharmacokinetics of meperidine is highly variable in neonates and infants. Half-life ranged from 3.3–59.4 hours in 21 infants.[12] Clearance increased with increasing BSA; however, half-life was not different among term infants <1 week of age, term infants >3 weeks of age (26–150 days of age), and preterm neonates (3.6–65 days of age).

Meropenem

Brand names

Merrem

Medication error potential

Look-alike, sound-alike drug names.

USP reports confusion with ertapenem, metronidazole, and midazolam.[1]

Contraindications and warnings

Contraindications: In patients with a hypersensitivity to meropenem or to other carbapenems or in patients who have had anaphylactic reactions to beta-lactams.[2]

Warnings

Allergic reactions: Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[2] These are more likely in patients who are sensitive to multiple allergens or other beta-lactams.[2]

Seizures: Neurotoxicity of the carbapenem antibiotics has been reported.[2] Seizures occur most commonly in patients with renal impairment and/or underlying neurologic disorders. (See Rare Adverse Effects in the Comments section.)

Superinfection: Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea, which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] Antibiotic use that is not for the treatment of *C. difficile* may need to be discontinued.[2]

Infusion-related cautions

If a decision is made to give meropenem to a patient with known penicillin, cephalosporins or beta-lactam hypersensitivity, the patient should be closely observed for allergenicity.[2]

May cause phlebitis at the injection site.[2]

Dosage

Neonates: *(Safety and effectiveness have not been established for patients <3 months of age.[2] Little dosing information is available in this age group.)*

Based on postnatal age (PNA)

≤7 days: 30–40 mg/kg/day divided q 12 hr over 15–30 minutes.[3,4]

>7 days: 40 mg/kg/day divided q 8 hr over 15–30 minutes.[4]

Based on weeks gestational age (WGA) and PNA for non-CNS infections[5]:

	<14 Days Old	**≥14 Days Old**
<32 WGA	40 mg/kg/day divided q 12 hr	60 mg/kg/day divided q 8 hr
≥32 WGA	60 mg/kg/day divided q 8 hr	90 mg/kg/day divided q 8 hr

A 15-day-old premature neonate (33 WGA; 1.59 kg) was given 120 mg/kg/day divided q 8 hr for 8 weeks as treatment for a brain abscess.[6] Another premature (34 WGA) neonate received meropenem at an unspecified dose for 6 weeks for a brain abscess.[7]

Infants and children

Complicated skin and skin structure infection: 30 mg/kg/day divided q 8 hr up to 1.5 g/day.[2]

Non-CNS infection: 60 mg/kg/day divided q 8 hr up to 3 g/day.[2,8]

CNS infection: 120 mg/kg/day divided q 8 hr up to 6 g/day.[2,6,8,9]

Dosage adjustment in organ dysfunction

If CrCl is 30–50 mL/min, give 20–40 mg/kg/day divided q 12 hr; if CrCl is 10–29 mL/min, give 10–20 mg/kg/day divided q 12 hr; if CrCl is <10 mL/min, give 10–20 mg/kg q 24 hr.[10]

Meropenem

Maximum dosage	120 mg/kg/day up to 6 g/day.[2,9–11]
Additives	Contains 3.92 mEq sodium/g of meropenem.[12]
Suitable diluents	D5W, D10W, NS, ½NS, D5NS, D5½NS, D5¼NS, D5LR, LR. Mannitol 2.5%, 5% sodium bicarbonate.[2,12]
Maximum concentration	50 mg/mL.[2,12]
Preparation and delivery	**Stability:** 1–4 hours at controlled room temperature and up to 4–24 hours if refrigerated.[2,12] Variable stability based on storage conditions and diluent; hence, consult appropriate reference for detailed information. **Compatibility:** See Appendix D for PN compatibility information.[13]
IV push	50 mg/mL over 3–5 minutes.[2,12]
Intermittent infusion	50 mg/mL over 15–30 minutes.[2,12]
Continuous infusion	Not generally done. Meropenem has been administered as a 3-hour infusion for the treatment of CNS infections.[14,15] Additionally, 24-hour continuous infusions have been used in the treatment of critically ill *adults.*[16–18] Pharmacokinetic studies in premature and full-term neonates and children have recommended a 3- to 4-hr infusion to attain target serum concentrations.[19,20]
Other routes of administration	IM administration has been used in the treatment of urinary tract infections and pneumonia in *adults.*[21]
Comments	**Rare adverse effects:** Neurotoxicity of the carbapenem antibiotics has been reported.[22,23] Seizures appear to be related to an underlying CNS disorder, impaired renal function, and/or large doses.[2] If seizures occur, the need for meropenem should be considered and the dosage should be assessed.[2] Thrombocytopenia has been reported in patients with renal dysfunction who are receiving meropenem.[2] An increase in alkaline phosphatase occurred in cystic fibrosis patients.[24] **Drug interactions:** Carbapenems may reduce serum concentrations of valproic acid, which can result in a loss of seizure control.[2,25] Serum valproic acid concentrations should be monitored frequently after beginning or increasing the dose of a carbapenem. Alternative antibiotics or anticonvulsant therapy should be considered if serum valproic acid concentrations drop below the therapeutic range or a seizure occurs.

Methotrexate

Brand names	Folex, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that methotrexate (MTX) has been confused with methylprednisolone sodium succinate, metolazone, metronidazole, mercaptopurine, and mitoxantrone; no patient harm resulted. USP also reports that MTX has been confused with minoxidil; patient harm resulted.[2] ISMP reports that Folex has been confused with Foltx.[3]
Contraindications and warnings	**U.S. boxed warning:** Administer under the supervision of a physician with experience in antimetabolite therapy. Because of the toxic and potentially life-threatening toxicity associated with MTX, it should only be used in life-threatening neoplastic disease or in patients with severe, recalcitrant psoriasis or rheumatoid arthritis unresponsive to other therapies.[4] MTX may cause serious neoplastic disease (malignant lymphoma) and increased risk of death. It has also been associated with tumor lysis syndrome and serious immune suppression, bone marrow suppression, and liver, lung, and kidney toxicities. May cause fetal death or congenital abnormalities when given to pregnant women. MTX also associated with life-threatening diarrhea/stomatitis, dermatologic reactions, and opportunistic infections.[4,5] Use caution when administering MTX concurrently with other hepatotoxic and nephrotoxic agents. Concurrent use with nonsteroidal anti-inflammatory drugs (NSAIDs); may cause serious adverse events (bone marrow suppression, aplastic anemia, and GI toxicity).[4,5] Use with radiotherapy may increase risk of soft tissue necrosis and osteonecrosis.[4] MTX elimination is decreased in patients with renal insufficiency, ascites, or pleural effusions; use cautiously with increased monitoring for toxicity in these patients.[4] High-dose regimens for osteosarcoma require considerable caution. (See Infusion-Related Cautions section.) Other high-dose therapies should be considered investigational.[4] MTX formulations containing preservatives must be not be used intrathecally or as high-dose therapy.[4,5] Use caution when administering high-dose MTX to patients receiving proton pump inhibitors (PPIs). Use of PPIs with MTX may lead to elevated serum levels of MTX and an increased risk of MTX toxicity.[4] **Contraindications:** Hypersensitivity to MTX or any component of the formulation, severe renal or hepatic impairment, pre-existing profound bone marrow suppression, alcoholic liver disease, AIDS, and pre-existing blood dyscrasias.[4,5] **Other warnings:** Neurotoxicity leading to seizures has been reported in pediatric acute lymphoblastic leukemia (ALL) patients.[4,5]
Infusion-related cautions	Aggressive hydration should accompany administration. (See Significant Adverse Effects in the Comments section.) Two patients experienced anaphylactoid reactions to high-dose MTX and BCG injections for osteosarcoma.[6]
Dosage	Consult protocol for complete information regarding MTX and leucovorin dosages, hydration, and alkalinization. MTX is used for a variety of neoplastic disease states.

Dosage *(cont.)*

Cancer

ALL

High-dose therapy: Loading dose of 200 mg/m^2.[7,8] This is generally followed by 0.8–5 g/m^2/day infused over 2–24 hr for 2–3 weeks.[7–10] Although doses as large as 33.6 g/m^2 have been infused over 4–48 hours,[11–13] outcomes were not substantially improved over those noted with lower doses (1.2 g/m^2).[7]

Maintenance therapy: 20–50 mg/m^2 IV weekly.[7,14] Adjust dose to maintain a specific WBC count.

Lymphoma: 30 mg/m^2 IV push,[15] 300 mg/m^2 IV infusion over 4 hr,[16] 1 g/m^2[17] up to 10 g/m^2 administered over 3–24 hr,[18] 3–30 mg/kg[16] up to 50–200 mg/kg infused over 3–6 hr.[19]

Meningeal leukemia: Doses administered every 2–5 days until cerebrospinal fluid normal, followed by weekly dose for 2 weeks, followed by monthly dose. IT doses in pediatric patients should be based on age (not body surface area [BSA]) as follows[20]:

Age (years)	IT Dose (mg)
<1	6
1	8
2	10
≥3	12

Only preservative-free MTX should be used for IT administration.[21]

Osteosarcoma: 1.25–15 g/m^2 infused over 4–6 hr.[22–25]

Juvenile rheumatoid arthritis: 0.8–1.1 mg/kg/week,[26] 15 mg/m^2/week,[27] up to 40 mg/m^2/week.[28] Generally given orally or IM.

Dosage adjustment in organ dysfunction

Adjust dosage in patients with renal dysfunction. If CrCl is 10–50 mL/min, give 50% of a normal dose; if CrCl is <10 mL/min, do not administer.[29]

Patients with renal dysfunction or those demonstrating toxicity with previous doses of intrathecal MTX may require leucovorin rescue in small doses.[30,31] Hemodialysis has limited usefulness in lowering plasma MTX in patients with renal failure,[32] but hemodialysis in combination with charcoal hemoperfusion has been successful in managing a patient with severe renal failure following high-dose MTX.[33] Oral administration of activated charcoal may be effective in lowering plasma MTX concentrations.[34]

Maximum dosage

Doses >100 mg/m^2 should be administered with leucovorin.[35] When given with leucovorin rescue, MTX may be escalated to the dosage that yields the best therapeutic effect.[35] Maximum IT dosage is 15 mg.[20]

Additives

MTX sodium for injection contains 0.43, 0.86, and 2.15 mEq sodium in sizes 2, 4, and 10 mL, respectively. The lyophilized product contains 7 mEq sodium per 1-g vial.[4,21]

May contain benzyl alcohol.[4,21] (See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.)

Suitable diluents

D5NS, D5W, NS.[4,21]

Maximum concentration

<25 mg/mL for IV or IM administration; 1 mg/mL for IT administration.[21]

Methotrexate

Preparation and delivery	Incompatible with fluorouracil, cytarabine, prednisolone, and sodium phosphate.[5] For PN compatibility information, please see Appendix C.
IV push	<25 mg/mL. May be administered by this method.[4,5,21]
Intermittent infusion	<25 mg/mL. May be administered by this method.[4,5,16–18,21]
Continuous infusion	<25 mg/mL. Doses >100–300 mg/m^2 are generally administered by continuous infusion.[4,5,11–13,18,21]
Other routes of administration	May be administered IM, intra-arterial, and IT.[4,5,21] IT doses should be with a preservative-free product diluted to 1 mg/mL using an appropriate sterile preservative-free diluent such as sodium chloride injection.[21]
Comments	**Significant adverse effects:** The administration of MTX has been associated with fatal pulmonary toxicity,[36] erythema and desquamation,[37] and death related to high doses.[25,38] Pulmonary toxicity may occur with low doses and be rapidly progressive.[4] Aggressive hydration from 100 mL/m^2/hr to 200 mL/m^2/hr during and after MTX must be administered in patients receiving intermediate to high doses of MTX to improve clearance and minimize toxicity.[9,13,35,39–43] Urinary alkalinization (pH >6.5) should be maintained during high-dose infusions of MTX and for 48 hours after infusion.[9,35,39–44] Leucovorin should be administered with MTX when doses are ≥100 mg/m^2 and should be dosed according to the patient's protocol and the amount of MTX given.[35,39] Leucovorin dosages should be modified if MTX clearance is delayed.[35,39] Clinical features known to place patients at risk for increased MTX toxicity include renal dysfunction,[41] dehydration,[25] vomiting,[13,41,45] diarrhea,[45] decreased urine flow,[46] urine pH below 6.5,[13,41,46] pleural effusions,[47,48] GI obstruction,[49] ascites,[47,48] concomitant use of nephrotoxic medications (e.g., amphotericin B and acyclovir),[13] previous history of cisplatin use,[50] Down syndrome,[51] and drug interactions decreasing elimination of MTX (e.g., salicylates,[52] omeprazole,[53] NSAIDs,[54–56] sulfamethoxazole/trimethoprim,[57] probenecid,[52,58] and penicillins).[59] MTX (250–1000 mg/m^2) is associated with a moderate (30% to 90%) risk of emesis.[60] Patients should receive antiemetic therapy to prevent acute and delayed nausea and vomiting. The recommended therapy is a 5HT3 receptor antagonist in combination with dexamethasone on every day that chemotherapy is administered.[60,61] These agents may be continued for up to 4 days after chemotherapy for the prevention of delayed nausea and vomiting. MTX (50 mg/m^2 to <250 mg/m^2) is associated with a low (10% to 30%) risk of emesis.[60] Patients should receive antiemetic therapy to prevent acute nausea and vomiting. The recommended therapy is a corticosteroid on every day chemotherapy is administered; alternatives are a phenothiazine (e.g., prochlorperazine) or a butyrophenone (e.g., droperidol).[60,61] Therapy for delayed nausea and vomiting is generally not needed. MTX (<50 mg/m^2) is associated with a minimal (<10%) risk of emesis.[60] Generally, prophylaxis for acute and delayed emesis is not needed. Patients may receive one-time prophylaxis with a phenothiazine (e.g., prochlorperazine) or a butyrophenone (e.g., droperidol).[60,61] Breakthrough medications for nausea and vomiting should be offered to patients receiving any dose of MTX. Appropriate medications include a phenothiazine (e.g., prochlorperazine), a butyrophenone (e.g., droperidol), a substituted benzamide (e.g., metoclopramide), or a benzodiazepine (e.g., lorazepam). Selection should be based on what the patient is currently receiving for acute anti-emesis prophylaxis.[60,61]

Comments *(cont.)*

Monitoring: Monitoring should include liver function tests, CBC with platelets, renal function tests, and chest x-ray.[4,5]

MTX serum concentrations should be monitored when administering large doses of drug. The relationship between serum concentration and toxicity is well established.[25,35,40,44] Recommended procedure is to monitor concentrations at 23 hours and 44 hours, and until concentrations decrease to <0.05 µmol/L.

Drug interactions: Because MTX is associated with numerous drug interactions,[4,5] consult appropriate resources for dosing recommendations before combining any drug with MTX.

Methyldopate HCl

Brand names	Aldomet, generic
Medication error potential	Look-alike, sound-alike drug names. Aldomet has been confused with Aldactone, but no patient harm resulted.[1]
Contraindications and warnings	**Contraindications:** Active hepatic disease (hepatitis, cirrhosis), liver disorders previously associated with methyldopate, hypersensitivity to methyldopate or any of its components, including sulfites, and therapy with monoamine oxidase inhibitors.[2] **Warnings:** Methyldopate therapy has been associated with a positive Coombs test, hemolytic anemia, and liver disorders; these may be fatal if not identified and managed appropriately.[2] (See Comments section.)
Infusion-related cautions	The injectable product contains sodium bisulfite and anaphylaxis may occur.[2] (See Additives section.)
Dosage	A decrease in blood pressure generally occurs within 4–6 hours and lasts 10–16 hours.[2,3] **Hypertensive crisis or emergency** **Initial dose:** 2–4 mg/kg/dose; if no effect within 4–6 hours, double the dose.[4] **Maintenance dose:** 5–50 mg/kg/day (usually 20–40 mg/kg/day) divided q 6 hr[3,5] or 0.6–1.2 g/m^2/day divided q 6 hr.[3] In hypertensive emergencies, blood pressure should be frequently monitored to ensure that it does not decrease too quickly.[3,6] One group recommended that the blood pressure decrease by one-third of the desired total blood pressure decrease within 6 hours, a further one-third decrease within the next 24–36 hours, with the final one-third decrease achieved over the next 48–72 hours.[7] Alternatively, a blood pressure decrease of $<$25% within minutes to 1 hour followed by further decreases over the next 2–6 hours if the patient is stable has been suggested.[3]
Dosage adjustment in organ dysfunction	Active metabolite may accumulate in uremia.[3] Adjust dosage in patients with renal dysfunction.[8] If CrCl is 10–50 mL/min, administer normal dose q 8–12 hr; if CrCl is $<$10 mL/min, give normal dose q 12–24 hr.[8]
Maximum dosage	65 mg/kg/day,[2,3] not to exceed 3 g/day or 2 g/m^2/day[2,3] or 1 g/dose.[9] The maximum *adult* dose recommended by the manufacturer is 1 g q 6 hr.[3]
Additives	Each mL contains 3.2 mg sodium bisulfite and 1.5 mg methylparaben and 0.2 mg propylparaben.[2] (See Appendix C for more specific information about potential adverse effects of sulfites and parabens.)
Suitable diluents	D5W.[2,3,10]
Maximum concentration	10 mg/mL.[2,3,10]

Methyldopate HCl

Preparation and delivery	**Stability:** Store intact vials at controlled room temperature and protected from freezing.[10] Oxidation of the catechol ring causes inactivation and dark-colored solution.[10] The rate of oxidation increases with increasing oxygen supply, increasing pH, and decreasing drug concentration.[10] **Compatibility:** For PN compatibility information, please see Appendix D.
IV push	Not recommended.[3]
Intermittent infusion	To avoid a paradoxical pressor effect, dilute in 50–100 mL D5W (≤10 mg/mL) and infuse slowly over 30–60 minutes.[3,4,10]
Continuous infusion	No information available to support administration by this method.
Other routes of administration	IM and SC administration are not recommended due to erratic absorption.[3,10]
Comments	**Significant adverse effects:** May cause hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.[3] May cause positive Coombs test; if evidence of hemolytic anemia, the drug should be discontinued.[3] **Monitoring:** CBC at baseline and periodically during therapy; Coombs test at baseline and at 6 and 12 months of therapy; liver function tests at baseline over the first 6–12 weeks of therapy; and any time there is unexplained fever.[2] **Other:** May cause urine to be discolored (pink/red to darkened).[2,3] A paradoxical pressor response has been reported.[4]

MethylPREDNISolone Sodium Succinate

Brand names	A-METHAPRED, Solu-Medrol, generic
Medication error potential	Look-alike, sound-alike drug names. ISMP reports that Solu-Medrol has been confused with Depo-Medrol and Solu-Cortef.[1] USP reports that Solu-Medrol has been confused with salmeterol and Solu-Cortef and no patient harm occurred. Solu-Medrol has been confused with Depo-Medrol and patient harm resulted.[2] USP reports that methylPREDNISolone sodium succinate has been confused with hydrocortisone sodium succinate, methotrexate, metoclopramide, metronidazole, and prednisolone sodium phosphate and no patient harm occurred. MethylPREDNISolone sodium succinate has been confused with methylPREDNISolone acetate and patient harm resulted.[2]
Contraindications and warnings	**Contraindications:** Neonates (products with benzyl alcohol), patients with systemic fungal infections, and patients with hypersensitivity to any component in the product.[3] Live virus (live attenuated influenza; measles, mumps, and rubella [MMR]; oral polio; varicella; rotavirus, smallpox; zoster) vaccinations should not be given during treatment with immunosuppressive doses of glucocorticoids.[4] (See Drug Interactions in the Comments section.) **Warnings:** Anaphylactoid reactions have been reported, and those with a prior history of such reactions require appropriate precautions.[3,5–8] Patients on chronic steroid therapy may require increased doses during stress.[3] Supraphysiologic doses of corticosteroids may result in suppressed pituitary-adrenal function, so therapy of more than a few days should be decreased gradually.[3,9,10] Immunosuppression and an increased risk for infection are possible during steroid therapy.[3]
Infusion-related cautions	Large doses should be infused slowly (over at least 30 minutes or 1 hour). Cardiac arrhythmias and cardiac arrest has been reported within minutes or hours of infusion in *adults* receiving ≥500 mg over <10 minutes.[11–13]
Dosage	Doses are based on severity of disease and patient response. The lowest dose that results in the desired effect should be used.[3,11] **Dosing adjustment for obesity:** In *adult* otherwise healthy obese volunteers, volume of distribution at steady state (Vss) was closely associated with ideal body weight, and clearance was reduced by 40% compared to nonobese *adults*. Suggested dosing alterations included dosing based on ideal body weight, with consideration for lengthening dosing intervals.[14] **Anti-inflammatory/immunosuppressive therapy:** 0.11–1.6 mg/kg/day divided q 6–8 hr.[3] **"Pulse" or high-dose anti-inflammatory therapy:** 10–30 mg/kg/day either daily for 3–6 days or every other day for 3–6 doses[15–20] or 600 mg/m^2/day for 3 days.[21] **Asthma exacerbations (ED or hospital treatment regimens):** Continue therapy until peak expiratory flow is 70% of predicted or personal best.[22] **<12 years old:** 1–2 mg/kg/day (max 60 mg/day) divided q 12–24 hr. **≥12 years old:** 40–80 mg/day divided q 12–24 hr. **Idiopathic thrombocytopenic purpura:** 30 mg/kg/dose daily for 3 days.[23]

MethylPREDNISolone Sodium Succinate

Dosage *(cont.)*

***Pneumocystis carinii* pneumonia**

Infants and children: 4–8 mg/kg/day divided q 6–12 hr for 5–7 days followed by oral prednisone.[24–26] CDC/NIH/IDSA/AAP guidelines recommend the following regimen as an adjunct to antibacterials in children infected with or exposed to HIV: 1 mg/kg/dose q 6 hr (days 1–7), 1 mg/kg/dose q 12 hr (days 8–9), 0.5 mg/kg/dose q 12 hr (days 10–11), 1 mg/kg/dose every day (days 12–16).[27]

Adolescents and *adults*: CDC/NIH/IDSA guidelines recommend the following regimen as an adjunct to antibacterials in patients infected with or exposed to HIV: 30 mg q 12 hr (days 1–5), 30 mg every day (days 6–10), and 15 mg every day (days 11–21).[28,29]

Spinal cord injury: A loading dose of 30 mg/kg over 15 minutes followed in 45 minutes by a continuous infusion of 5.4 mg/kg/hr × 23 hr (if started within 3 hours of injury) or × 48 hr (if started 3–8 hr after injury).[30,31] Although the National Acute Spinal Cord Injury trial did not include any patients <13 years old,[31] some pediatric clinicians have adopted this practice,[32,33] while others have abandoned the practice.[34,35] The *adult* Consortium for Spinal Cord Medicine no longer recommends steroids for acute spinal cord injury due to the lack of definitive evidence showing efficacy and the risk of significant adverse events.[36]

Other uses

Acute disseminated encephalomyelitis: 10–30 mg/kg/day[37,38] (1 g in patients >30 kg)[38] for 3–5 consecutive days, usually followed by an oral steroid taper for 4–6 weeks.

Chronic interstitial lung disease: 300 mg/m^2/day for 3 days, repeated q 4–6 wk.[39]

Lupus nephritis: 30 mg/kg every other day for 6 doses.[40]

Periocular hemangiomas of infancy: 2 mg/kg/dose q 12 hr for 2 days, then transitioned to an oral corticosteroid taper resulted in rapid hemangioma shrinkage and visual improvement in 15 infants.[41] Oral prednisolone (n = 10) was as effective as pulse high-dose IV methylPREDNISolone (n = 10) in problematic infantile hemangiomas.[42]

Pulmonary hemorrhage: 2–4 mg/kg/day.[43]

Ventricular tachycardia/silent lymphocytic myocarditis: 30 mg/kg/day for 3 days.[44]

Dosage adjustment in organ dysfunction

Those with cirrhosis of the liver or who are hypothyroid may have an exaggerated response.[3] Dosing adjustment is not necessary for renal dysfunction.[45]

Maximum dosage

30 mg/kg,[19] 30 mg/kg rounded to 250 mg, 500 mg, 1 g, or 2 g,[15,17] or up to 3 g/dose[18] has been used as pulse therapy for severe glomerulonephritis, systemic lupus erythematosus, and renal transplant rejection.

Additives

Some products contain benzyl alcohol.[3] (See Appendix C for more specific information about potential benzyl alcohol toxicity in neonates.)

Contains 2.01 mEq sodium/g of methylPREDNISolonesodium succinate.[11,46]

Suitable diluents

D5W, D5NS, D5½NS, LR, NS.[46]

Maximum concentration

125 mg/mL for IV push.[11]

MethylPREDNISolone Sodium Succinate

Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.
IV push	Over 1 to several minutes.[3,11] High doses (≥15 mg/kg; ≥500 mg/dose) should be infused over ≥30 minutes.[3,11]
Intermittent infusion	Over 20–60 minutes.[3]
Continuous infusion	May be infused continuously.[11,30,31]
Other routes of administration	May be administered IM.[3,11]
Comments	**Other/Kawasaki disease:** An early study found 30 mg/kg methylPREDNISolone as an initial treatment of Kawasaki disease (in combination with IV immunoglobulin [IVIG] and aspirin) resulted in faster resolution of fever, improvement in inflammatory markers, and shorter hospital stay.[47] A randomized, multicenter trial of 198 patients found no benefit of adding methylPREDNISolone to IVIG in all patients diagnosed with Kawasaki disease,[48] but a pilot study found that 48 patients predicted to have refractory Kawasaki disease responded favorably to the addition of 30 mg/kg methylPREDNISolone to the standard IVIG and aspirin regimen (86.4% remained afebrile for 36 hours after treatment versus 23.1% who received standard therapy without methylPREDNISolone, P <.001).[49] A case report described a child with Kawasaki disease who had a severe rash similar to Stevens-Johnson syndrome (without mucosal involvement) who failed to respond to three IVIG treatments but was felt to respond after three methylPREDNISolone doses of 30 mg/kg.[50] **Adverse effects:** Intractable hiccups, palpitations, and anaphylaxis have been reported.[6,8,51] Additionally, atrial fibrillation,[52] seizures, transient blindness,[53] and fatal varicella[54] have occurred after methylPREDNISolone administration. Children with a history of drug-induced cutaneous reactions are more likely to have an adverse reaction to IV corticosteroids.[55] Corticosteroid-induced bronchospasm with methylPREDNISolone in an *adult* with severe asthma was reported. The author recommended considering corticosteroids as a contributing factor in asthmatics who do not improve on IV steroids (especially if aspirin allergy is also present). Skin testing may help guide safe alternative corticosteroids.[56] A pediatric study looking at effects of short-term (3 days) methylPREDNISolone 2 mg/kg/day on bone metabolism in infants and children reported significant, but reversible, inhibition of bone formation markers.[57] A 14-year-old male with nephrotic syndrome being treated with oral prednisolone developed Stevens-Johnson syndrome. The boy was changed to IV methylPREDNISolone 20 mg/kg/dose every other day. By day 2 of treatment, fever subsided and by the fifth day the bullae began to subside.[58] **Drug interactions:** Drugs that enhance hepatic clearance (e.g., phenytoin, phenobarbital, carbamazepine, rifampin) may decrease blood levels and lessen physiologic activity of methylPREDNISolone.[3] Live virus vaccines may be given 1 month after ending a ≥2-week course of high-dose systemic corticosteroids (2 mg/kg/day of prednisone or its equivalent; or 20 mg/day if >10 kg.[59]

Metoclopramide HCl

Brand names	Reglan, generic
Medication error potential	Look-alike, sound-alike drug names. Metoclopramide has been confused with methocarbamol, methylprednisolone sodium succinate, metolazone, metoprolol tartrate, and trimethobenzamide. Reglan has been confused with Regitine, Regonol, Relafen, Renagel, Requip, Robaxin, and Zofran; no patient harm resulted.[1] Confused with metronidazole resulted in patient harm resulted.[1]
Contraindications and warnings	**U.S. boxed warning:** Because long-term therapy and total cumulative dose are associated with an increased risk of tardive dyskinesia, metoclopramide should not be continue beyond 12 weeks, unless benefits of continued therapy clearly outweigh the risk of tardive dyskinesia.[2] Metoclopramide therapy should be discontinued in patients who develop signs or symptoms of tardive dyskinesia as there is no known treatment for tardive dyskinesia. In some patients, symptoms may lessen or resolve after metoclopramide treatment is stopped.[2] **Contraindications:** Known hypersensitivity to metoclopramide or any of its components, patients with pheochromocytoma, patients with epilepsy or patients on medications that cause extrapyramidal symptoms, and when a decrease in GI motility would be dangerous.[3] **Other warnings:** Extrapyramidal symptoms, tardive dyskinesia and neuroleptic malignant syndrome may develop during metoclopramide therapy. Dystonias and other extrapyramidal symptoms more commonly develop in pediatric patients.[3]
Infusion-related cautions	Rapid administration may result in anxiety, restlessness, and drowsiness.[3]
Dosage	**Emetogenic cancer chemotherapy:** 1–3 mg/kg 30 minutes prior to chemotherapy, with repeat doses q 2–3 hr for 8–12 hours.[3–5] Pretreatment with diphenhydramine may decrease the likelihood of extrapyramidal side effects seen with this dose.[3] One study used 0.4 mg/kg/hr for 6 hours in a 2-year-old boy.[6] (See Comments section.) In *adults,* a bolus of 0.6–3.5 mg/kg 30 minutes prior to cisplatin infusion followed by 0.5 mg/kg/hr for 8 hours has been used.[7,8] **Gastroesophageal reflux:** 0.4–0.8 mg/kg/day divided q 6–8 hr.[9,10] **Hypomotility:** 0.1 mg/kg q 4–6 hr up to 0.5 mg/kg/day.[11] **Persistent vomiting due to acute gastroenteritis:** 0.3 mg/kg to a maximum of 10 mg.[12,13] Cochrane Database review noted that metoclopramide reduced the number of episodes of vomiting and hospital admission.[13] **Postsurgical nausea and vomiting prophylaxis:** 0.15–0.5 mg/kg up to 10 mg as a single dose infused after anesthesia induction or on arrival in the recovery room.[14–16] Repeat q 6–8 hr PRN. Studies comparing metoclopramide to ondansetron for postoperative emesis after strabismus surgery[17,18] and post-tonsillectomy/adenotonsillectomy[19,20] have found ondansetron to be more effective. **Small bowel intubation (single dose only)[3]** **<6 years:** 0.1 mg/kg.[3] **6–14 years:** 2.5–5 mg.[3] **>14 years:** 10 mg.[3]

Dosage adjustment in organ dysfunction	The labeling recommends a 50% decrease in dose if CrCl <40 mL/min.[3] Another reference recommends adjustment of dose in patients with renal dysfunction as follows[21]: if CrCl is 30–50 mL/min, give 75% of a normal dose; if it is 10–29 mL/min, give 50% of a normal dose; and if CrCl is <10 mL/min, give 25% of a normal dose. Supplement doses above for hemodialysis and peritoneal dialysis (25% of a normal dose) and continuous renal replacement therapy (75% of a normal dose).[21]
Maximum dosage	**Emetogenic cancer chemotherapy:** 2 mg/kg when chemotherapy is started followed by doses of 2 mg/kg 2, 6, and 12 hours later.[5] In *adults,* 4 mg/kg as single dose[22] or 2 mg/kg q 2–3 hr for a total of 10 mg/kg over 8.5 hours.[23]
Additives	Each mL contains 8.5 mg NaCl.[24]
Suitable diluents	D5W, D5½NS, NS, LR, R.[3,24]
Maximum concentration	5 mg/mL.[24]
Preparation and delivery	For PN compatibility information, please see Appendix D.
IV push	5 mg/mL over 1–2 minutes in *adults* receiving a dose of 10 mg.[3,24]
Intermittent infusion	Dilute doses >10 mg in 50 mL of a compatible fluid and infuse over ≥15 minutes.[3,24]
Continuous infusion	Dilute doses >10 mg in at least 50 mL of a compatible fluid.[3,24] NS is the preferred diluent due to the stability of the solution.[3]
Other routes of administration	Solution of 5 mg/mL may be given via IM administration.[3]
Comments	**Significant adverse effects:** Neonates are more susceptible to methemoglobinemia during metoclopramide use.[3,9] Children are also more likely than *adults* to experience acute dystonic reactions; these reactions occur more frequently at larger doses.[3,4,25] A bolus of 2.5 mg/kg followed by a continuous infusion of 0.4 mg/kg/hr resulted in a dystonic reaction (urinary retention) after 6 hours in a child receiving chemotherapy.[6] Diphenhydramine (0.5–1 mg/kg) has been used to treat these reactions.[23,25,26] Gynecomastia related to metoclopramide use has been reported in pediatric patients.[27] **Drug interactions:** Metoclopramide is associated with numerous drug interactions.[3] Consult appropriate resources for dosing recommendations before combining any drug with metoclopramide. **Other:** Metoclopramide has been used for bedside transpyloric tube placement in pediatric ICU patients[28] and more recently to ease discomfort while placing nasogastric tubes in *adults*.[29] Metoclopramide (0.05 mg/kg/dose given q 8 hr) has been given to a small group of preterm infants (mean gestation 29 weeks) for approximately 3 weeks. No adverse effects were documented.[30]

MetroNIDAZOLE/MetroNIDAZOLE HCl

Brand names

Flagyl IV RTU (metroNIDAZOLE), MetroNIDAZOLE Injection (metroNIDAZOLE), Flagyl IV (metroNIDAZOLE HCl)

Medication error potential

ISMP's *Confused Drug Names* lists confusion with metformin.[1]

USP reports confusion with fluconazole, mebendazole, meropenem, metformin, methocarbamol, methotrexate, methylprednisolone sodium succinate, metoclopramide, miconazole, omeprazole, and potassium chloride. Confusion with metformin and metoclopramide has resulted in patient harm.[2]

Contraindications and warnings

U.S. boxed warning: Known to be carcinogenic in mice and rats.[3] Avoid unnecessary use and reserve for indicated conditions.[3]

Contraindications: In patients with a prior history of hypersensitivity to metroNIDAZOLE or other nitroimidazole derivatives.[3]

Other warnings: Convulsive seizures and peripheral neuropathy have been reported. The appearance of abnormal neurologic signs should be assessed and therapy discontinued as required.[3] (See Rare Adverse Effects in the Comments section.)

Infusion-related cautions

None.

Dosage

Neonates: One report advocates a loading dose of 15 mg/kg.[4]

PNA	<1200 g	1200–2000 g	≥2000 g
<7 days	7.5 mg/kg q 24–48 hr[5,6]*	7.5–15 mg/kg q 24 hr[5,6]	15 mg/kg/day divided q 12 hr[6,7]
≥7 days		15 mg/kg/day divided q 12 hr[6]	30 mg/kg/day divided q 12 hr[6]

*Until 4 weeks of age.

Although doses of 22.5 mg/kg/day divided q 8 hr have been given for 5 days without problems, the authors suggested that less frequent dosing would be appropriate in newborns.[8,9]

Infants and children: For mild-to-moderate infections, give 15–50 mg/kg/day divided q 6–8 hr up to 2.25 g/day.[6,10] Not indicated for severe infections.[6]

***Clostridium difficile* infection:** 30 mg/kg/day divided q 6 hr for 10 days.[6]

Surgical: 30 mg/kg divided into 3 doses postoperatively in gangrenous appendicitis.[11]

Dosage adjustment in organ dysfunction

If CrCl is <10 mL/min, give 16 mg/kg/day divided q 6 hr.[12] Use a lower than recommended dose in patients with severe hepatic disease due to accumulation of metroNIDAZOLE and its metabolites in the plasma.[3]

Maximum dosage

4 g/day.[3]

Additives

14 mEq of sodium/500 mg of metroNIDAZOLE.[3,13]

Suitable diluents

None recommended.

Maximum concentration

5 mg/mL.[3,13]

MetroNIDAZOLE/MetroNIDAZOLE HCl

Preparation and delivery	**Delivery system issues:** Do not use with aluminum containing equipment, including needles.[3] **Compatibility:** See Appendix D for PN compatibility information.[14]
IV push	Not recommended.[3]
Intermittent infusion	Over 60 minutes.[13]
Continuous infusion	May be used.[3,13]
Other routes of administration	None.

Comments

Seizures may occur with large cumulative doses and prolonged use. The cumulative dose is the most important factor in the pathogenesis of seizures.[15] In cases involving *adults* the cumulative dose has been >40 g. No correlation has been noted between this adverse effect and serum concentration of metroNIDAZOLE.[16]

Neuropathy has been reported when cumulative doses exceed 30 g.[17] It is usually reversible when the drug is discontinued.[18] Continuation of therapy, even at a lower dose, may potentiate symptoms.[17]

MetroNIDAZOLE is a nitroimidazole and should be used cautiously in patients with evidence of or history of blood dyscrasia. Although a mild leukopenia has been observed, no persistent hematologic abnormalities have been seen in clinical studies.[3]

Monitoring: Total and differential leukocyte counts before and after therapy.

Drug interactions: MetroNIDAZOLE inhibits alcohol dehydrogenase and other alcohol oxidizing enzymes to produce a disulfiram-type reaction (e.g., flushing, sweating, headache, and tachycardia) in patients who are concurrently given ethanol. Shown to potentiate the anticoagulant effect of warfarin and can result in an increase in prothrombin time.[3] Consult appropriate resources for dosing recommendations before combining any drug with metroNIDAZOLE.

Laboratory interference: MetroNIDAZOLE may interfere with some assays to decrease values for aspartate aminotransaminase, alanine transaminase, lactate dehydrogenase, triglycerides, or glucose.[3]

Micafungin

Brand names	Mycamine
Medication error potential	None reported by ISMP or USP.[1–3]
Contraindications and warnings	**Contraindications:** Patients with known hypersensitivity to the drug, any of its components, or other echinocandins.[4] **Warnings:** Hypersensitivity reactions (see Infusion-Related Cautions section), hematologic effects (acute intravascular hemolysis, hemoglobinuria, hemolytic anemia), abnormalities in liver function tests, hepatitis and hepatic failure, and renal dysfunction and acute renal failure have been reported.[4] Postmarketing reports have described cases of Stevens Johnson syndrome, toxic epidermal necrolysis, and disseminated intravascular coagulation.[5]
Infusion-related cautions	Phlebitis and thrombophlebitis have been reported and occur more frequently with administration via a peripheral line.[4] Rapid infusions may result in histamine-mediated reactions.[4] Isolated cases of serious hypersensitivity/anaphylaxis have also occurred.[4]
Dosage	Experience with micafungin in children, particularly neonates, is limited[4,6]; currently there is no established dose range for pediatric patients. **Treatment:** Premature neonates (weight >1000 g) have received 0.75–3 mg/kg in a single-dose pharmacokinetic and safety study.[7] A small group of young infants have received doses as high as 10 mg/kg/day.[8] (See below, and Pharmacokinetic Considerations in the Comments section.) **Infants and children:** 1.5–12 mg/kg given once daily.[6,9–16] Larger doses may be necessary for children <8 years of age secondary to increased clearance.[6,17,18] (See Pharmacokinetic Considerations in the Comments section.) Some papers dosed micafungin on patient weight as follows: **≤40 kg:** 1.5–2 mg/kg/day (up to 75 mg/day).[13,15,16] **>40 kg:** 75–100 mg/day.[13,16] If infection or signs and symptoms persisted, dose has been increased every 1–7 days by 1.5 mg/kg (up to 75 mg) increments in patients ≤40 kg and by increments of 75–100 mg in patients >40 kg.[13,16] One study dosed micafungin based on patient weight and fungal species as follows[10]: **<40 kg:** 1 mg/kg/day (*Candida albicans*) or 2 mg/kg/day (nonalbicans or germ-tube negative). **≥40 kg:** 50 mg/day (*Candida albicans*) or 100 mg/day (nonalbicans or germ-tube negative). The dose was increased by increments of 50 mg (1 mg/kg for patients <40 kg) at 5 days if disease was stable or progressive.[10] One study examined the benefit of high doses of micafungin given to young infants, most of <34 weeks gestational age. Six infants weighing <1000 g (mean 688 g) received 10 mg/kg/day for 4–6 days. Seven infants weighing >1000 g (mean 2101 g) were treated with 7 mg/kg/day for 4–6 days. All patients achieved targeted AUC_{0-24} by day 4 of treatment; few adverse events were attributed to the drug. One patient received 7 mg/kg/day for a total duration of 33 days without adverse event.[8]

Dosage *(cont.)*	**Prophylaxis:** 1 mg/kg given once daily (studies in transplant patients).[19,20] 3 mg/kg given every other day to children 10 years of age and under who were undergoing stem-cell transplant resulted in trough serum concentrations of at least 0.3 mcg/mL. This regimen was judged to be a suitable alternative to other prophylactic regimens in this population.[21]
Dosage adjustment in organ dysfunction	No dosage adjustment necessary for renal dysfunction or in mild, moderate, or severe hepatic impairment.[4,15,22–24] Continuous veno-venous hemofiltration has little effect on micafungin kinetics; no dose adjustment or modification recommended.[20]
Maximum dosage	150 mg/day in *adults.*[4,6] One study in three patients reported the use of up to 200 mg/day.[10] Doses as high as 10 mg/kg/day have been used in neonates.[8]
Additives	None.
Suitable diluents	D5W, NS.[4,25]
Maximum concentration	1.5 mg/mL.[4]
Preparation and delivery	NS recommended for reconstitution. D5W may also be used. Do not use diluents containing a bacteriostatic agent for reconstitution.[4,25] Further dilute reconstituted micafungin in a suitable diluent to a final concentration of 0.5–1.5 mg/mL.[4] Flush an existing line with NS prior to micafungin infusion.[4,25] Do not mix or infuse with other medications.[5] Y-site administration compatibility has been demonstrated with a number of medications.[25]
IV push	Not recommended.[4]
Intermittent infusion	0.5–1.5 mg/mL; infuse over 1 hour.[4]
Continuous infusion	No information available to support administration by this method.
Other routes of administration	No information available to support administration by other routes.
Comments	**Significant adverse effects:** Adverse effects most commonly occurring in one pediatric study were elevations in serum transaminases and alkaline phosphatase, hyperbilirubinemia, and nausea.[15] Arrhythmias and hypotension have been reported in *adults*.[4] **Drug interactions:** Micafungin is a poor substrate for the CYP3A4 isoenzyme and is associated with the potential for drug interactions. Concomitant administration of micafungin may cause sirolimus, itraconazole, or nifedipine toxicity, and dosage of sirolimus, itraconazole, or nifedipine should be reduced, if necessary. Consult appropriate resources for dosing recommendations before combining any drug with micafungin.[3,15] **Pharmacokinetic considerations:** One neonatal study compared three dosing regimens (0.75, 1.5, and 3 mg/kg/day) in two infant weight groups (500–1000 g and >1000 g). Infants <1000 g only received 0.75 mg/kg per dose. The smaller infants had decreased serum concentrations and increased clearance when compared to the larger infants.[7]

Midazolam HCl

Brand names	Versed
Medication error potential	High-alert medication (moderate sedation agent, IV) that has an increased risk of significant harm if it is used in error.[1] Look-alike, sound-alike drug names. Confusion has been reported with diazepam and lorazepam[2] and between Versed and Valium, VePesid, and Vistaril.[2]
Contraindications and warnings	**U.S. boxed warning:** Respiratory depression and arrest may occur, especially when used for sedation in noncritical care settings.[3] If not recognized promptly and treated effectively, death or hypoxic encephalopathy may occur.[3] Should only be used in settings that can continuously monitor respiratory and cardiac function. For deeply sedated pediatric patients, a dedicated individual, other than the practitioner performing the procedure, should monitor the patient throughout the procedures. Oxygen, resuscitative drugs, age- and size-appropriate equipment for bag/valve/mask ventilation and intubation, and skilled personnel for the maintenance of a patent airway and support of ventilation must be immediately availability.[3] Should not be administered by rapid injection to neonates as severe hypotension and seizures have been reported, particularly when fentanyl is given concomitantly.[3] The use of the 1-mg/mL formulation or dilution of the 1- or 5-mg/mL formulation is recommended to facilitate slower injection.[3] **Contraindications:** In patients with a known hypersensitivity to midazolam (or any other benzodiazepines), or any component of the formulation.[3] Although benzodiazepines are contraindicated in patients with acute narrow-angle glaucoma, they may be used in patients with open-angle glaucoma provided they are receiving appropriate therapy.[3] **Other warnings:** Do not use in patients with shock or coma if vital signs are decreased, or in acute alcohol intoxication with depression of vital signs.[3] Use cautiously in patients with uncompensated acute illnesses (e.g., severe fluid or electrolyte disturbances).[3]
Infusion-related cautions	Respiratory depression and arrest requiring mechanical ventilation may occur following excessive dosing, rapid administration,[3] or use with fentanyl.[3,4] This is especially true in neonates who may develop profound and/or prolonged respiratory effects and hypotension when administered rapidly.[3] Avoid intra-arterial injection or extravasation.[3]
Dosage	Flumazenil should be readily available for reversal. (See Other in the Comments section and Flumazenil monograph.) The dose should be calculated using ideal body weight in obese patients.[3] (See Appendix B.) Children <6 years of age may require larger doses (mg/kg) than older pediatric patients and *adults.*[3] Allow 3–5 minutes after dose to achieve peak CNS effect.[3] **Anesthesia induction:** 0.15 mg/kg followed by up to 3 doses of 0.05 mg/kg at 2-minute intervals.[5] Time to induction was shorter with a dose of 0.3 mg/kg.[6] Doses of 0.6 mg/kg did not reliably induce anesthesia in children given atropine and meperidine.[7] **Procedural sedation:** Midazolam is the preferred benzodiazepine because of its rapid onset following IV administration of 2–5 minutes (IM 10–20 minutes) and short duration of 30–60 minutes (IM 45–120 minutes.[8–10] It does not possess analgesic activity and must be combined with other agents (i.e., fentanyl) when analgesia is needed.[10] 0.05–0.4 mg/kg immediately before the procedure then q 2–5 min to desired effect.[9,11–15] Doses up to 2 mg/dose[15,16] or 5 mg/dose[11,13] and a total of 10 mg have been used.[16] Some recommend age dependent dosing: 0.05–0.1 mg/kg titrating up to 0.6 mg/kg (0.5–5 years) or 0.025–0.05 mg/kg titrating up to 0.4 mg/kg (6–12 years).[8,9,16]

Dosage *(cont.)*	**Sedation with mechanical ventilation:** Because hypotension may occur following a loading dose in neonates, some recommend that one not be given. If one is used some suggest that the continuous infusion be given at a faster rate for the first several hours.[17] 0.1–0.2 mg/kg over 2–5 minutes,[17–23] followed by 0.03–0.4 mg/kg/hr.[17–21] Some recommend 0.03 mg/kg/hr for those <32 weeks gestational age and 0.06 mg/kg/hr for those older than 32 weeks.[19] **Status epilepticus:** Tachyphylaxis may require progressively larger dose within the first 24–48 hours.[24] A loading dose of 0.02–0.6 mg/kg[22,24–35] followed by a continuous infusion of 0.04–3 mg/kg/hr.[22,24–35] Titrate by 0.06 mg/kg/hr q 15 min.[28] Mean maintenance infusion ranged from 0.14–3 mg/kg/hr.[22,24–35] In a report of 306 pediatric patients, the dose was <0.4 mg/kg/hr in 81% of patients.[31] Most patients regain full consciousness by an averaged 4 hours after discontinuation of midazolam.[35]
Dosage adjustment in organ dysfunction	Adjust dosage in patients with hepatic dysfunction.[3] Patients with chronic renal failure and/or congestive heart failure eliminate midazolam more slowly, but no dosage adjustment is required in renal dysfunction.[36] (See Drug Delivery Issues in the Preparation and Delivery section.)
Maximum dosage	Total doses >5 mg are not usually necessary for conscious sedation in *adults*.[3] For anesthesia induction, single doses of ≤0.6 mg/kg.[5,6] not to exceed 5 mg/dose have been used.[11,13] The largest dose given by continuous infusion was 3 mg/kg/hr.[26]
Additives	0.14 mEq (0.8%) sodium per mL.[37] Some products also contains 0.01% disodium edetate, and benzyl alcohol 1%, with hydrochloric acid and, if necessary, sodium hydroxide to adjust the pH.[37] Preservative-free midazolam hydrochloride is also available. (See Appendix C for specific information about benzyl alcohol's potential for toxicity.)
Suitable diluents	D5W, NS, D5NS.[37] Use preservative-free SW for dilution in neonates.
Maximum concentration	<5 mg/mL for IV push[3,4] and 1 mg/mL for IM administration.[3]
Preparation and delivery	**Preparation:** To minimize excipient load, preservative-free preparations should be used. If this is not possible, use the 5 mg/mL product and dilute to 0.5 mg/mL with SW without preservatives.[37] **Stability:** Midazolam is a colorless to light yellow solution. It should be stored at room temperature.[37] Frozen product is physically stable for 3 days after thawing at room temperature thawing.[37] **Delivery system issues:** Patients receiving extracorporeal membrane oxygenation (ECMO) may require larger doses due to drug absorption in the ECMO circuit.[38] Midazolam was stable in polypropylene syringes stored at room temperature, not exposed to direct light, for 10 days, 13 days, 36 days, and 4 weeks.[37] No significant sorption was noted when administered by PVC, glass, and polyethylene-lined laminated container.[37] **Compatibility:** For PN compatibility, please see Appendix D. **Photosensitivity:** For long-term stability, protect from light.[37] Provided the solution is prepared with compatible solutions it does not require protection for short-term storage and administration.[37]
IV push	1 or 5 mg/mL given over 20–30 seconds for anesthesia induction.[3,6] Rapid administration (<2 minutes) may cause severe hypotension in neonates, especially if concurrent fentanyl is given.[3] Seizures have also been reported in neonates following rapid administration.[3]

Midazolam HCl

Intermittent infusion	≥2 minutes.[3]
Continuous infusion[41]	Diluted to a concentration of 0.5 mg/mL with NS or D5W.[3]
Other routes of administration	1 mg/mL.[3] IM doses of 0.15–0.5 mg/kg (maximum total dose 10 mg) have been administered safely in children requiring sedation or in patients in status epilepticus.[39,40] Although a 20% failure rate was noted when IM administration was given prehospitalization,[40] it is now considered the benzodiazepine of choice for IM and prehospital administration in *adults*.[41] Has been given by buccal administration.

Comments

Rare adverse effects: Paradoxical reactions, such as hyperactive, agitations, or aggressive behavior, have been reported with benzodiazepines, particularly in adolescent/pediatric or psychiatric patients.[3]

Involuntary epileptiform movements may occur in preterm infants <32-weeks-old.[42–45] Brief tonic-clonic seizures have occurred in patients with atypical absence (petit mal) status epilepticus.[3] Seizure activity and myoclonus have also been reported, especially in very low birth weight neonates.[3,42,44,46] The movements generally began a few minutes after a bolus injection and continue for several hours.[44,46]

Drug interactions: Midazolam is a substrate of CYP2B6 and 3A4 (major) and is a weak inhibitor of CYP2C8, 2C9, and 3A4.[47] Consult appropriate resources for dosing recommendations before combining any drug with midazolam.

Pharmacodynamic considerations: Rapid administration or large doses may decrease blood pressure and cerebral blood flow velocity.[48] For this reason, midazolam should be used cautiously in neonates.

Other: A withdrawal syndrome may begin 24 hours after cessation of prolonged continuous infusion (i.e., >5–10 days of continual use).[43,49–51] Cumulative doses above 60 mg/kg are correlated with withdrawal syndromes.[52] When weaning off midazolam, decrease dose by 0.06–0.12 mg/kg/hr q 15 min.[28]

Some practitioners recommend weaning a patient from midazolam to oral lorazepam.[53]

Midazolam Rate	Equivalent Oral Dose of Lorazepam
1 mcg/kg/min = 1.44 mg/kg/day	0.3 mg/kg/day = 0.1 mg/kg q 8 hr
2 mcg/kg/min = 2.88 mg/kg/day	0.6 mg/kg/day = 0.1–0.15 mg/kg q 6 hr
3 mcg/kg/min = 4.32 mg/kg/day	0.9 mg/kg/day = 0.1–0.15 mg/kg q 4–6 hr
4 mcg/kg/min = 5.76 mg/kg/day	0.3 mg/kg/day = 0.15 mg/kg q 4 hr

Source: From Cyndi Reid, PharmD, Department of Pharmaceutical Services, Children's Hospital of Michigan, Detroit, MI.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for complete or partial reversal of benzodiazepine toxicity.[54] (See Flumazenil monograph.)

Milrinone Lactate

Brand names

Primacor

Medication error potential

High-alert medication (inotropic medication, IV) that has an increased risk of causing significant patient harm if it is used in error.[1]

Look-alike, sound-alike drug names. Confusion has been reported for Primacor with Natrecor.[2]

Contraindications and warnings

Contraindications: Hypersensitivity to milrinone, any component, or inamrinone (amrinone).[3]

Warnings: Regardless of route or method of delivery, milrinone has not been shown to be safe or effective when used longer than 48 hours in patients with heart failure.[3] (See Other in the Comments section.) It should *not* be used in patients with severe obstructive aortic or pulmonic valvular disease[3] and may aggravate outflow tract obstruction in those with hypertrophic subaortic stenosis.[3] Use caution if vigorous diuretic therapy has been used or has been suspected of causing significant decreases in cardiac-filling pressure.[3]

Infusion-related cautions

Spontaneous bronchospasm has been reported.[3] IV site should be monitored and extravasation should be avoided.

Dosage

The dosage and side effect profile have not been established for pediatric patient patients.

Hemodynamic support (including septic shock)

Loading dose: 50 mcg/kg administered over 10–60 minutes.[4] Doses of 50–100 mcg/kg have been used.[4–11] The loading dose has been given over 3 hours.[12–14]

Continuous infusion: 0.25–0.75 mcg/kg/min. Doses of 0.2–1.2 mcg/kg/min[4–16] have been used and should be titrated to desired effect. One group recommends that for every increase of 0.25 mcg/kg/min, a bolus of 25 mcg/kg be given.[9] Another suggests that in the postoperative setting, if renal function is impaired, that the initial dosages not exceed 0.2 mcg/kg/min.[11]

Loading dose of 25 mcg/kg over 10 minutes followed by doses up to 0.75 mcg/kg/min have been used specifically to decreased the risk of peripheral necrosis (i.e., toes) associated with meningococcal sepsis.[15]

Prevention of postoperative low cardiac output syndrome

Premature neonates: A study in 29 premature neonates (<29 weeks) found that a loading dose of 0.75 mcg/kg over 3 hours, followed by 0.2 mcg/kg/min for 18 hours effectively prevented low systemic blood flow.[14] Conversely, a randomized, placebo-controlled study involving 90 premature infants (<30 weeks) found that the same regimen did *not* prevent low systemic blood flow during the first 24 hours; hence, milrinone should *not* be used for that purpose.[12]

Full-term neonates, infants, and children: A loading dose of 75 mcg/kg administered over 60 minutes followed by a continuous IV infusion of 0.75 mcg/kg/min for 35 hours was used in a randomized, placebo-controlled trial of 227 patients (age: 2 days to 6.9 years; median: 3 months).[17] These large doses of milrinone significantly reduced the risk of low cardiac output syndrome by 64%.[17]

A prospective, open-label trial compared a small dose of milrinone to a larger dose.[10] The small dose group (n=11) was given 25 mcg/kg over 5 minutes followed by 0.25 mcg/kg/min; 30 minutes later, a second 25 mcg/kg was given and the infusion was increased to 0.5 mcg/kg/minute. The large dose group (n=8) received a loading dose of 50 mcg/kg over 10 minutes followed by 0.5 mcg/kg/min; 30 minutes later, a second dose of 25 mcg/kg was given and the rate was increased to 0.75 mcg/kg/min. A third loading dose of 25 mcg/kg was given to either group if needed. Using NONMEM analysis (two-compartment model), the following were recommended: 104 mcg/kg loading dose followed by an infusion of 0.49 mcg/kg/min in infants and 67 mcg/kg loading dose followed by an infusion of 0.61 mcg/kg/min in children.

Dosage *(cont.)*

Pulmonary hypertension (PPHN)

A Cochran Review assessed published and quasi randomized controlled trials that compared milrinone with placebo, inhaled nitric oxide (iNO), or potential treatments other than iNO in neonates with PPHN.[18] The authors concluded that the efficacy and safety of milrinone in the treatment of PPHN is unknown.

Six infants with chronic heart disease and severe pulmonary hypertension were studied. Within 72 hours of beginning milrinone, there was a significant increase in early diastolic myocardial velocities in the right ventricle, accompanied by increasing systolic velocities in the right ventricle and interventricular septum. Oxygenation index was significantly reduced, blood pressure unchanged, and ductal shunt velocity minimally altered over the same time period.[19] Successful use of 50 mcg/kg followed by 0.2 mcg/kg/min has also been given to a term newborn.[20]

Dosage adjustment in organ dysfunction

Adjust dosage in renal dysfunction (see below) as impaired milrinone clearance may result in significant hypotension.[3]

CrCl (mL/min)	Dose (mcg/kg/min)	CrCl (mL/min)	Dose (mcg/kg/min)
5	0.2	30	0.33
10	0.23	40	0.38
20	0.28	50	0.43

Maximum dosage

A loading dose of 100 mcg/kg[3] and a maintenance dose of 1.2 mcg/kg/min in infants and children.[16]

Additives

None reported.

Suitable diluents

D5W, NS, LR, ½NS.[21]

Maximum concentration

Loading dose may be given undiluted[3] but may be diluted to allow for ease of administration. Normal dilution is 200 mcg/mL,[21] but 250 mcg/mL have been used for continuous infusion.[21] One study noted stability of a solution of 400 mcg/mL in RL, D5W, ½NS, and NS.[22]

Preparation and delivery

Stability: Stable at 0.2 mg/mL for 72 hours at room temperature in normal light.[21] Avoid freezing.[21]

Compatibility: A precipitate will form when furosemide is injected into an IV line infusing milrinone.[3,18,21] See more specific references for other drug incompatibilities. (See Appendix D for PN compatibility information.)

IV push

Milrinone has been given over 30 seconds,[12] but most suggest a longer infusion time.[3,21]

Intermittent infusion

Most references suggest that the loading dose should be given over 10–60 minutes.[4,21] One group has consistently reported infusing the loading dose over 3 hours.[12–14]

Continuous infusion

≤200 mcg/mL.[3,21]

Milrinone Lactate

Other routes of administration	Has been given by IO administration.[4]

Comments

Rare adverse effects: Discontinue therapy if dose-related elevations in liver function test occur and clinical symptoms of hepatotoxicity are note.[23]

Hypokalemia and hypomagnesemia may occur.[23]

Monitoring: Milrinone is a positive inotrope and vasodilator that has little chronotropic activity.[23] It does produce a slight shortening of an atrioventricular (AV) node conduction time, indicating a potential for an increased ventricular response rate.[3] ECG should be monitored during infusion for supraventricular and ventricular arrhythmias.[3] Blood pressure and heart rate should be monitored during the infusion. If the patient develops excessive hypotension, the infusion should be decreased or stopped.[3] Fluid status should be monitored and diuretic and electrolyte therapy adjusted PRN. Monitor alanine aminotransferase and aspartate aminotransferase.

Drug interactions: Consult appropriate resources before combining any drug with milrinone.

Pharmacokinetic considerations: Half-life in very preterm infants was more than 10 hours, which is considerably longer than that reported for infants and children.[14]

Other: In a multicenter trial of 1088 patients with Class III and IV heart failure, long-term *oral* therapy showed no improvement in symptoms and an increased risk of hospitalization and sudden death.[3] In this study, patients with Class IV symptoms appeared to be at particular risk of life-threatening cardiovascular reactions. There is no evidence that milrinone given by long-term continuous or intermittent infusion does not carry a similar risk.

Mivacurium

Brand names	Mivacron, generic; all formulations have been removed from the U.S. market.[1] (See Comments section.)
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[2]
Contraindications and warnings	**Contraindications:** Hypersensitivity to mivacurium or any of its components.[3] Multiple-dose vials are contraindicated for use in neonates due to the benzyl alcohol preservative.[3] **Warnings:** Use carefully under the supervision of experienced clinicians; personnel should be skilled in airway management, resuscitation, and respiratory support. Intubation and ventilatory support equipment, including oxygen therapy, should be readily available. Reversal agents should be readily available when giving mivacurium.[3] Use with caution in patients with known or suspected homozygous atypical plasma cholinesterase gene.[3]
Infusion-related cautions	Hypersensitivity reactions, hypotension, arrhythmias, and bronchospasm have been reported.[3] Histamine release is dose- and infusion-rate related. In patients with clinically significant cardiovascular disease or any history suggestive of an increased sensitivity to histamine (e.g., asthma), the initial dose should be reduced and administered over 1 minute.[3] (See Dosing section.)
Dosage	*Respiratory function must be supported during use of this agent. Concurrent administration of a sedative is also necessary. Monitoring of neuromuscular transmission with a peripheral nerve stimulator is recommended during continuous infusion or with repeated dosing.*[3,4] **Dosing adjustment for obesity:** Obese patients (≥30% of ideal body weight) should be dosed on ideal body weight.[3] (See Appendix B.) **Induction and maintenance of neuromuscular blockade** **Patients with significant cardiovascular disease or any history suggestive of histamine sensitivity:** 0.15 mg/kg infused over 1 minute.[3] **Neonates, for nonemergent intubation:** 0.2 mg/kg.[5] (Other agents are preferred; see Comments section.) **Children 2–14 years of age:** 0.2 mg/kg repeated PRN to maintain pharmacological paralysis.[3,6–9] May follow initial dose by continuous infusion of 5–31 mcg/kg/min.[3,6,8]
Dosage adjustment in organ dysfunction	Standard doses may be used in patients with renal or hepatic dysfunction. Compared to healthy patients, the duration of neuromuscular blockade with mivacurium will be approximately 1.5 times longer in severe renal impairment and 3 times longer in end-stage liver disease.[3] Infusion rates should be decreased by 50% in patients with hepatic disease.[3] The manufacturer suggests that no adjustment is necessary in patients with renal dysfunction[3]; however, another reference suggests giving 50% of the usual dose in *adults* with any of the following: CrCl ≤50 mL/min, requiring peritoneal dialysis, or undergoing continuous renal replacement therapy.[10]
Maximum dosage	Infusion rates as large as 31 mcg/kg/min have been used.[3]
Additives	May contain benzyl alcohol.[3] (See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.)

Mivacurium

Suitable diluents	D5W, D5NS, D5LR, LR, or NS.[3]
Maximum concentration	2 mg/mL.[3]
Preparation and delivery	Mivacurium is an acidic solution; do not administer with alkaline solutions.[3]
IV push	2 mg/mL over 5–15 seconds.[3] In patients with clinically significant cardiovascular disease or any history suggestive of an increased sensitivity to histamine (e.g., asthma), the initial dose should be reduced and administered over 1 minute.[3]
Intermittent infusion	Not administered by this method.
Continuous infusion	0.5–2 mg/mL.[3]
Other routes of administration	Not administered via other routes.
Comments	**Other:** For neonatal nonemergent intubations, AAP recommends that vagolytic and muscle relaxant agents should be considered and that analgesic agents or anesthetic doses of a hypnotic agent should be administered. Rocuronium or vecuronium is preferred over other available neuromuscular blocking agents.[11] **Significant adverse effects:** Mivacurium formulations are no longer marketed in the United States,[1] reportedly due to its risk of histamine release and bronchospasm.[11] Prolonged paralysis has been reported after mivacurium administration in pediatric and *adult* patients with reduced plasma cholinesterase activity.[3,12,13] **Drug interactions:** Concomitant administration of other drugs (e.g., aminoglycosides, clindamycin, inhalational anesthetics, ketamine, magnesium, quinidine, or succinylcholine) may prolong neuromuscular blockade.[3] Consult appropriate resources for additional information on drug interactions.

Morphine Sulfate

Brand names	Generics; Astramorph PF, DepoDur PF (extended-release liposome epidural injection), Duramorph PF, Infumorph (preservative-free for microinfusion devices only)
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP reports that morphine has been confused with HYDROmorphone.[2] USP reports that morphine sulfate has been confused with HYDROmorphone, magnesium sulfate, methadone, and OxyContin.[3] Patient harm resulted when morphine sulfate was confused with meperidine.[3]
Contraindications and warnings	**U.S. boxed warning:** Because of the risk for severe adverse effects with the epidural or IT routes of preservative-free morphine, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose.[4] Naloxone (opioid antagonist) injection and resuscitative equipment should be immediately available in case of life-threatening or intolerable side effects and whenever IT or epidural preservative-free morphine therapy is being initiated.[4] **Contraindications:** Those with known hypersensitivity to morphine should not receive morphine sulfate.[4,5] A manufacturer of generic morphine lists convulsive states (morphine stimulates the spinal cord), heart failure resulting from chronic lung disease, cardiac arrhythmias, and brain tumor as contraindications.[6] Those with acute bronchial asthma or upper airway obstruction should not receive morphine.[4,5] **Other warnings:** Products containing preservatives (generics) are not for IT or epidural use.[6] Some products are for use with specific patient controlled analgesia pumps or auto-injectors. Morphine sulfate is available in a variety of concentrations ranging from 0.5–50 mg/mL.[7] Choose products carefully. Errors in programming patient-controlled analgesia pumps, including the substitution of a more concentrated product than the pump was programmed to infuse, have resulted in deaths.[8] The respiratory depressant effects of morphine and its ability to increase intracranial pressure may be exaggerated in patients with head injury.[6] IT use has been associated with a higher incidence of respiratory depression than epidural use.[4]
Infusion-related cautions	Confirm the choice of the correct morphine product and concentration on the vial prior to use. Respiratory depression and arrest requiring mechanical ventilation may occur and is reversible with naloxone.[9,10] This is more likely to occur with rapid administration.[6] Rapid IV administration may result in chest wall rigidity.[4,11]
Dosage	*Dosing is titrated to effect and the lowest effective dose should be used. Chronic opioid use results in tolerance and an increased dose requirement. In these patients, a weaning protocol should be implemented when morphine is discontinued to avoid withdrawal symptoms.* **Neonates (preservative-free morphine):** 0.05–0.1 mg/kg IV/IM once as premedication for nonemergent intubation[10]; 0.05 mg/kg IV, IM or SC q 4–6 hr (max 0.1 mg/kg/dose); continuous infusion of 0.001–0.03 mg/kg/hr.[12–19] Based on achieving a therapeutic morphine concentration of 15 ng/mL, an infusion of 0.0075 mg/kg/hr would be appropriate at term birth and 0.0125 mg/kg/hr at 1 month of age.[20,21] Of note, a decreased gestational age and postconceptional age are directly related to clearance.[15,16,18,19] (See Comments section.)

Dosage *(cont.)*

Infants/children: 0.05–0.2 mg/kg (usual max doses: infants, 2 mg/dose; children <6 years, 4 mg/dose; children 7–12 years, 8 mg/dose; adolescents, 15 mg/dose) q 2–4 hr PRN[11,12,16,17,21–25] or continuous infusion of 0.005–0.03 mg/kg/hr that may be preceded by a bolus.[16,17,21,23,25,26] A systematic review of sedation regimens to facilitate mechanical ventilation in the pediatric ICU reported bolus doses of 0.05–0.1 mg/kg with continuous infusions of 0.01–0.06 mg/kg/hr.[27]

Sickle cell disease with pain crisis: 0.1–0.15 mg/kg q 2–4 hr usual starting dose in opioid-naïve patients.[28] Bolus of 0.15 mg/kg followed by a continuous infusion of 0.03–0.15 mg/kg/hr achieved adequate analgesia in hospitalized children.[29] Of note, a pharmacokinetic study found an eightfold variability in clearance in 18 children that resulted in a larger dose requirement (without increased side effects) in some patients.[30] This may be due to anemia-related changes in hepatic blood flow that accelerate renal or hepatic clearance.

Severe pain: Larger doses may be needed in cancer, burn, or other patients with severe pain. In eight children with terminal malignancy, continuous infusions ranging from 0.03–0.15 mg/kg/hr provided adequate or complete pain relief.[31] However, doses from 0.76–2.6 mg/kg/hr were needed in two of these.

Patient-controlled analgesia[32]: The following are recommendations for treating acute pain in opioid-naïve *adults* and children with acute pain.

Children <50 kg

Usual starting dose (range): 0.02 mg/kg/dose (0.01–0.03 mg/kg/dose).

Usual starting lockout: 5 doses/hr; 6–8 minute lockout.

Usual basal or continuous rate: 0–0.03 mg/kg/hr.

***Adults* >50 kg**

Usual starting dose (range): 1 mg (0.5–2.5 mg).

Usual starting lockout (range): 6 minutes (5–10 minutes).

Epidural or IT use of preservative-free morphine (under the direction of a physician experienced in this technique)[4,5,9]

Epidural: 0.03–0.05 mg/kg up to 0.1 mg/kg or 5 mg/day.[25]

IT (usually 1/10th the epidural dose): Forty-six children from 12–17 years old undergoing spinal fusion who received either 0.005 mg/kg or 0.015 mg/kg (maximum dose 1 mg) preservative-free morphine with sufentanil intrathecally had decreased blood loss and postoperative need for opiates.[33]

Dosage adjustment in organ dysfunction

CrCl 10–50 mL/min/1.73 m²: 75% of the usual dose.[34]

CrCl ≤10 mL/min/1.73 m²: 50% of the usual dose.[34]

Use with caution in severe liver disease.[5,6,11]

During extracorporeal membrane oxygenation, dosage requirements are increased even though studies have shown that clearance is decreased because of binding to the PVC tubing and membrane oxygenator.[35,36]

Maximum dosage

0.2 mg/kg/dose up to 10 mg/dose[11] or 15 mg/dose.[25] In patients with sickle cell disease, continuous infusions as high as 0.2 mg/kg/hr have been reported.[30] With repeated dosing, tolerance can develop resulting in increased dosage requirements.

In *adults,* the epidural maximum single dose is 5 mg and maximum per 24 hours is 10 mg.[4,5,9] The IT dose is usually 1/10th of the epidural dose.[4,5,9]

Morphine Sulfate

Additives	Some morphine products contain chlorobutanol, phenol, sulfites, sodium phosphates, and/or formaldehyde sulfoxylate.[7] (See Appendix C for specific information about adverse effects.)
Suitable diluents	D5W, D10W, NS, ½NS, LR, R.[7] SW for immediate injection.[6]
Maximum concentration	Usually 1 mg/mL for continuous infusion.[7,25]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information.
IV push	0.5–5 mg/mL.[25] Over 4–5 minutes.[6,11]
Intermittent infusion	0.5–5 mg/mL.[25] 1 or 5 mg/mL using commercially-available solutions via a patient-controlled infusion device.[11] Over 15–30 minutes.[25] The ISMP and Vermont Oxford Network recommend a standard concentration of 0.1 mg/mL or 0.5 mg/mL for intermittent infusions in neonates.[37] Highly concentrated solutions (≥10 mg/mL) intended for epidural or IT use are not for IV, IM, or SC administration of individual doses due to the risk of substantial overdose, because the vials contain large amounts of morphine (200–500 mg per vial).[11]
Continuous infusion	0.1–1 mg/mL is typical but higher concentrations have been used.[7,11,25] The ISMP and Vermont Oxford Network recommend a standard concentration of 0.1 mg/mL for continuous infusions in neonates.[37]
Other routes of administration	May be given IM or SC.[6] The IM route is preferred when repeat doses are needed because SC dosing causes local tissue irritation and pain.[6] Only preservative-free products are given via the epidural or IT route.[4,5,38]
Comments	**Monitoring:** Patients should be monitored for adequacy of analgesia/sedation and signs and symptoms that would indicate toxicity such as decreased respiratory rate, oxygen saturation, and alertness. **Pharmacokinetics:** A pharmacokinetic study in 17 preterm neonates (26–34 weeks gestational age) found a morphine clearance of 2.4 mL/kg/min, half-life of 8.75 hours, and volume of distribution of 1.82 L/kg.[39] Another study comparing preterm with term neonates found no statistically significant difference in half-life between the two groups (10.6 ± 2.7 hr versus 7.6 ± 2.6 hr, respectively), clearance (2.23 ± 0.95 mL/kg/min versus 2.03 ± 1.46 mL/kg/min), and volume of distribution (2.04 ± 1.01 L/kg versus 2.07 ± 1.26 L/kg).[40] The age-related effects on morphine requirements and plasma concentrations of morphine and its metabolites were compared in postsurgical term infants from 0–4 weeks of age (n = 63), 4–26 weeks (n = 65), 26–52 weeks (n = 30), and 1–3 years (n = 39). All received a bolus of 0.1 mg/kg followed by a continuous infusion of 0.01 mg/kg/hr or 0.03 mg/kg/dose q 3 hr. At 24 hours after surgery, neonates had higher morphine, morphine-3-glucuronide, and morphine-6-glucuronide concentrations than the three older age groups indicating a capacity for glucuronidation and a lower renal clearance.[41] **Drug interactions:** Use morphine cautiously in patients receiving other CNS depressants as effects are additive.[6]

Multivitamins (Adult)

Brand names

MVI Adult, MVI Adult Unit Vial, MVI-12, Infuvite Adult

Medication error potential

None noted.

Contraindications and warnings

Contraindications: Known hypersensitivity to vitamins or excipients or pre-existing hypervitaminosis.[1,2]

Infusion-related cautions

Rapid administration may result in dizziness, faintness, and tissue irritation.[1,2]

Dosage

Children ≥11 years and *adults*: 5 mL/day from vial 1 and 5 mL/day from vial 2 of MVI Adult (contains 150 mcg vitamin K) or Infuvite Adult (contains 150 mcg vitamin K) or 10 mL/day of mixed MVI–12 Unit Vial (does not contain vitamin K).[1,2]

Pediatric vitamin shortages[3]: The A.S.P.E.N. 2006 Pediatric Multivitamin Task Force recommends that when a shortage is recognized, the pediatric multivitamins should be reserved for infants <2.5 kg or <36 weeks gestational age (WGA). Infants who are able to ingest 50% of their nutrient needs should be switched to oral vitamins. For those who must receive the parenteral product, the following doses of the *adult* parenteral multivitamins are recommended:

2.5 kg up to 11 years of age: Use 2 mL/kg up to half the *adult* dose (5 mL/day) and supplement vitamin K to a total dose of 200 mcg. (MVI Adult and Infuvite Adult contain 150 mcg of vitamin K; MVI–12 does not contain vitamin K.)

<2.5 kg or <36 WGA: If the Pediatric Multivitamin Product is unavailable, 1 mL/kg/day of an *adult* product. *Adult* multivitamins contain excipients that are known to be toxic in preterm infants. (See Additives section.)

Note: Vitamin K is not contained in MVI–12 but is included in the other products for use in *adults*.

Dosage adjustment in organ dysfunction

Hypervitaminosis A and D are potential complications in patients with renal failure.[1,2]

Maximum dosage

One-and-a-half to three times the usual daily dosage for 2 or more days for patients with multiple vitamin deficiencies or markedly increased requirements.[1,2,4] (See Comments section.)

Additives

The following excipients are included in the *adult* multivitamin products.[1–3] Infuvite Adult has been reformulated to contain less contaminant aluminum.

Product	Propylene Glycol	Polysorbate 80	Polysorbate 20	Aluminum Contaminant
MVI–Adult	3 g/10 mL	160 mg/10 mL	2.8 mg/10 mL	43–183 mcg/L
MVI–12	3 g/10 mL	160 mg/10 mL	2.8 mg/10 mL	43–78 mcg/L
Infuvite Adult	3 g/10 mL	140 mg/10 mL	None	70 mcg/L

See Appendix C for specific information about propylene glycol and polysorbate 80 potential adverse effects.

Suitable diluents

D5NS, D5W, D10W, D20W, LR, NS, PN solutions.[5]

Multivitamins (Adult)

Maximum concentration	Dilute dose in ≥500 mL of a compatible IV fluid.[1,2,5] Do not give undiluted.[1]
Preparation and delivery	**Stability:** Addition of these products to solutions containing bisulfites as antioxidants may result in thiamine inactivation.[6] **Photosensitivity:** Protect from light during storage.[1,5]
IV push	Contraindicated.[5]
Intermittent infusion	Over a number of hours.[4] However, the contents of MVI–12 vials 1 and 2 (5 mL each) were diluted in 50 mL D5W and administered over 20 minutes without adverse effects in normal *adult* volunteers.[7]
Continuous infusion	May be infused continuously as in PN solutions.[1,2]
Other routes of administration	Not indicated.
Comments	**Laboratory interference:** Ascorbic acid in the urine may cause false–negative urine glucose measurements.[1,2] **Monitoring:** For patients receiving larger doses than usual or who are on parenteral vitamins for 4–6 months, serum concentration measurement of vitamins A, C, D, and folic acid should be performed to ensure that concentrations are within the normal range.[1,2,8]

Multivitamins (Pediatric)

Brand names

MVI Pediatric, Infuvite Pediatric

Medication error potential

None noted.

Contraindications and warnings

Contraindications: Known hypersensitivity to vitamins or excipients or pre-existing hypervitaminosis.[1,2]

Infusion-related cautions

Rapid administration may result in dizziness, faintness, and tissue irritation.[1,2]

Dosage

Dosages listed are in terms of the reconstituted single dose 5-mL vial.

Neonates <1 kg: 1.5 mL/day[1–3] or 2 mL/kg/day.[4] (See Comments section.)

Neonates and infants 1–3 kg: 3.25 mL/day[1–3,5,6] or 2 mL/kg/day up to 5 mL/day.[4]

Infants and children ≥2.5 kg and <11 years: 5 mL/day.[1,2,4–6]

Dosage adjustment in organ dysfunction

Hypervitaminosis A and D are potential complications in patients with renal failure.[1,2]

Maximum dosage

Usually 5 mL. However, larger doses may be indicated during certain diseases.[1,2]

Additives

The following excipients are included in the pediatric multivitamin products.[1,2,7] Infuvite Pediatric has been reformulated to contain less contaminant aluminum.

Product	Propylene Glycol	Polysorbate 80	Polysorbate 20	Aluminum Contaminant
MVI–Pediatric	None	50 mg/5 mL	0.8 mg/5 mL	42 mcg/L
Infuvite Pediatric	None	59 mg/5 mL	None	30 mcg/L

Suitable diluents

D5NS, D5W, D10W, D20W, LR, NS, PN solutions.[8]

Maximum concentration

Dilute dose in ≥100 mL of compatible IV fluid.[1,2,8] Do not give undiluted.[1,2]

Preparation and delivery

Stability: Addition of these products to solutions containing bisulfites as antioxidants may result in thiamine inactivation.[9]

Photosensitivity: Protect from light during storage.[1,2,8] (See Comments section.)

IV push

Contraindicated.[1,2,8]

Intermittent infusion

Over a number of hours. Infants <6 months of age have received PN solutions (including micronutrients) cycled over 18 hours.[10]

Continuous infusion

May be infused continuously as in PN solutions.[1,2]

Other routes of administration	Not indicated.

Comments

May not result in optimal vitamin dosing in low birth weight infants.[3,4,11,12] Doses of 1.5 mL/day did not maintain vitamin E levels in therapeutic range (1–3 mg/dL) in 56% of infants <1 kg.[3,11] Doses of 2 mL/kg in premature infants will not provide adequate vitamin A.[4]

The addition of sulfites to PN solutions results in thiamine inactivation. However, sulfites may slow the peroxidation of vitamins exposed to light. Whether to cover PN solutions and tubing to protect from light particularly in preterm neonates has been debated.[8,13,14]

Laboratory interference: Ascorbic acid in the urine may cause false–negative urine glucose measurements.[1,2]

Muromonab-CD3

Brand names	Orthoclone OKT3
Medication error potential	None noted.
Contraindications and warnings	**U.S. boxed warning:** Only physicians experienced in immunosuppressive therapy and management of solid organ transplant patients should use muromonab-CD3.[1] Patients receiving muromonab-CD3 should be treated in facilities equipped and staffed for CPR and where the patient can be observed for an appropriate amount of time after infusion. Anaphylactic and anaphylactoid reactions may occur following infusion of any dose. Serious, occasionally life-threatening or lethal, systemic, cardiovascular, and CNS reactions have been reported and include pulmonary edema (especially in patients with volume overload), shock cardiovascular collapse, cardiac or respiratory arrest, seizures, coma, cerebral edema, cerebral herniation, blindness and paralysis. Fluid status should be carefully monitored prior to and during treatment. Methylprednisolone pretreatment is recommended to minimize these symptoms known as the cytokine-release syndrome. **Contraindications:** Patients who have hypersensitivity to muromonab-CD3 or products of murine origin, have antimouse antibody titers ≥1:1000, are in uncompensated heart failure or fluid overload, have uncontrolled hypertension, have a history of seizures, are who are pregnant or breastfeeding. **Other warnings:** Pediatric patients should be carefully evaluated for fluid retention and hypertension before initiating muromonab-CD3 due to the risk of cerebral edema and herniation.[1]
Infusion-related cautions	See Contraindications and Warnings section.
Dosage	**Transplant (rejection) (several different dosing strategies have been used)** **≤30 kg:** 2.5 mg/day for 10–14 days.[1–6] **>30 kg:** 5 mg/day for 10–14 days.[1–6] **<10 kg:** 1.25 mg/day for 10 days.[7] **≥10–30 kg:** 2.5 mg/day for 10 days.[7] **>30 kg:** 5 mg/day for 10 days.[7] **<20 kg:** 2.5 mg/day for 10–14 days.[8] **>20 kg:** 5 mg/day for 10–14 days.[8] 1 mg/10 kg/day (≤5 mg) for 10–14 days.[9] 0.1–0.2 mg/kg/day (≤5 mg) for 7–14 days.[10–12] CD3+ cell counts should be <25/mm^3 and OKT3 serum concentration ≥800 ng/mL in children.[1,2] **Acute viral myocarditis:** Five children (15 months to 16 years of age) with left ventricular ejection fractions of 5% to 20% were treated with a variable combination of corticosteroids, cyclosporine, azathioprine, IV immunoglobulin, and OKT3 dosed at 0.1 mg/kg/day for 10–14 days.[13]
Dosage adjustment in organ dysfunction	None noted.

Maximum dosage	15 mg.[1]
Additives	Contains polysorbate 80.[11] (See Appendix C for specific information about polysorbate adverse effects.)
Suitable diluents	None.
Maximum concentration	1 mg/mL.
Preparation and delivery	Do not shake solution.[1] Withdraw the solution from the ampule through a low protein-binding 0.2- or 0.22-micron filter. Discard this filter and attach a new needle prior to bolus injection.[1]
IV push	Over <1 minute.[1]
Intermittent infusion	Not indicated.[1]
Continuous infusion	Not indicated.
Other routes of administration	Not indicated.
Comments	**Monitoring:** Daily CD3+ T cells and OKT3 serum concentrations.[1,2,4–6,10,14,15]

Nafcillin Sodium

Brand names

Generic

Medication error potential

USP reports confusion with ampicillin, ampicillin and sulbactam, oxacillin, piperacillin and tazobactam.[1]

Contraindications and warnings

Warnings: Individuals who have a type I reaction to penicillin may have cross-sensitivity to cephalosporins.[2] (See Appendix C for specific information.)

Infusion-related cautions

If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity.[2] (See Comments section.)

Extravasation may cause tissue sloughing and necrosis.[2–4] (See Appendix E for management.)

Serious anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, and airway management.[2]

Dosage

Neonates

PNA	<1200 g	≤2000 g	>2000 g
≤7 days	50 mg/kg/day divided q 12 hr[5,6]*	50–100 mg/kg/day divided q 12 hr[5,6]	75 mg/kg/day divided q 8 hr[5]
>7 days	50–75 mg/kg/day divided q 12 hr[5,6]*	50–75 mg/kg/day divided q 6–8 hr[5,6]	100–140 mg/kg/day divided q 6 hr[5]

*Until 4 weeks of age.

Infants and children

Mild-to-moderate infections: 50–100 mg/kg/day divided q 6 hr.[5]

Severe infections: (e.g., meningitis, osteomyelitis, pericarditis,) 100–200 mg/kg/day divided q 4–6 hr.[5,7]

Endocarditis (oxacillin-susceptible): 200 mg/kg/day divided q 4–6 hr for 6 weeks (native valve) with or without gentamicin.[8] If prosthetic valve related, add gentamicin (3 mg/kg/day divided q 8 hr during the first 2 weeks of nafcillin) and oral rifampin (20 mg/kg/day divided q 8 hr for 6 weeks or longer).[8]

Dosage adjustment in organ dysfunction

No adjustment in either renal[9] or hepatic failure; however, the dosage should be adjusted in patients with combined renal and hepatic dysfunction.[2,10] If CrCl 10–29 mL/min, give 9–25 mg/kg q 6 hr; if CrCl < 10 mL/min, give 7.5–15 mg/kg q 6 hr.[10]

Maximum dosage

200 mg/kg/day; 18 g/day has been given to *adults* with severe infections.[11,12]

Additives

2.9 mEq sodium/g of nafcillin sodium.[2,13]

Suitable diluents

D5, D5½NS, NS, LR, ½NS, SW.[2,13]

Maximum concentration

40 mg/mL.[13] Maximum concentration of 64 mg/mL (NS), 71 mg/mL (D5), 128 mg/mL (SW) for peripheral infusion in fluid-restricted patients.[13,14]

Nafcillin Sodium

Preparation and delivery	**Delivery system issues:** The mixing of penicillins with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[13] (See Appendix C for more specific information.) **Compatibility:** See Appendix D for PN compatibility information.[15]
IV push	Appropriate dose in 15–30 mL of ½NS, NS, or SW over 5–10 minutes through running IV.[2,13]
Intermittent infusion	2–40 mg/mL infused over 30–60 minutes.[13]
Continuous infusion	Has been reported in a neonate.[16]
Other routes of administration	250 mg/mL in SW, BW, or NS by deep IM injection.[2]
Comments	**Rare adverse effects:** Has caused interstitial nephritis.[2]

Naloxone HCl

Brand names	Narcan
Medication error potential	Look-alike, sound-alike drug names. Narcan has been confused with Lanoxin, Norcuron, and Nubain.[1] Naloxone has been confused with nalbuphine and nalmefene.[2]
Contraindications and warnings	**Contraindications:** Hypersensitivity to naloxone or any component of the formulation.[3] **Warnings:** An acute abstinence syndrome can be precipitated by abrupt and complete reversal of narcotic effects.[3] Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on opioids. This includes newborns of mothers who are physically dependent on opioids. (See Other in the Comments section.) Naloxone is not effective in (1) treating respiratory depression due to nonopioid drugs; (2) the management of acute toxicity caused by levopropoxyphene; and (3) reversal of respiratory depression by partial agonists (e.g., buprenorphine) or mixed agonist/antagonists (e.g., pentazocine). In the case of partial agonists or mixed agonist/antagonists, reversal may be incomplete or may require larger doses due to the drugs prolonged duration, slow rate of binding, and slow dissociation from opioid receptor.[3]
Infusion-related cautions	None reported.
Dosage	*When used for acute opiate overdose, other resuscitative measures (e.g., maintenance of an adequate airway, artificial respiration, cardiac massage, vasopressor agents) should be readily available.* **Neonatal opioid depression/asphyxia:** There is no role for naloxone in the resuscitation of a newborn with intrauterine asphyxia, which is unrelated to opioid use. Naloxone may be used to treat asphyxia in a neonate whose mother was given opiates during labor and delivery. Although it has been given to the mother shortly before delivery, the duration of action only lasts for the first 2 hours of the neonates life; hence, it is preferable to treat the neonate after delivery.[3] 0.01 mg/kg (IV) administered into the umbilical vein and repeated q 2–3 min until clinical response; repeat q 20–60 min for 1–2 hours PRN.[3,4] Additional doses may be necessary at 1- to 2-hour intervals depending on the response of the neonate and the dosage and duration of action of the opiate administered to the mother. **Opiate intoxication/dependency (known or suspected):** Smaller doses may be used to reverse respiratory depression associated with therapeutic opioid use.[5] Repeat doses may be necessary, because the duration of action of some narcotics may exceed that of naloxone. Monitor for at least 24 hours because relapse may occur as naloxone is metabolized.[3] **<5 years or ≤20 kg (including neonates):** 0.1 mg/kg q 2–3 min PRN until opiate effects are reversed.[3,5–10] Repeat q 20–60 min for 1–2 hours if inadequate response or symptoms recur.[3] **5 years or >20 kg:** 2 mg/dose[3,5,8,11–13] with subsequent doses of 0.1 mg/kg q 1–2 min if no improvement occurs.[3,8,12,13] Repeat q 20–60 min if symptoms recur.[3] When repeated doses are required, some suggest the use of continuous infusion (i.e., 2.5–160 mcg/kg/hr).[14,15] After titrating clinical effectiveness, decrease by 25%.[14–16] Wean infusion in 50% increments over 6–12 hours, depending on the half-life of the opiate.[16]

Dosage *(cont.)*

Postoperative opioid respiratory depression: Abrupt reversal of postoperative opioid depression may cause nausea, vomiting, sweating, trembling, tachycardia, hypertension, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest, which has resulted in death.[3]

Dose used is the same as that given for opiate intoxication. 0.005–0.01 mg/kg q 2–3 min until clinical response is seen and then at 1- to 2-hour intervals as necessary.[3,16]

Septic shock: Dose and dosage regimens have not been established. Although naloxone causes a sustained increase in the blood pressure of those with septic shock,[17–19] it does not appear to improve survival.[20] To date, there have not been any controlled trials in children. Three case reports have described success with 0.01–0.05 mg/kg/dose intermittently in infants and children with septic shock secondary to *Neisseria meningitides, Escherichia coli,* and Group B *Streptococcus*.[14,21,22] Intermittent doses have been followed by infusions of 0.13–0.45 mg/kg/hr.[14]

Opioid-induced pruritus

Prevention: One double-blind prospective trial in 46 postoperative children (6–17 years old) used a continuous infusion of 0.25 mcg/kg/hr and found a lower incidence of adverse effects (nausea/vomiting, pruritus) without loss of pain control.[23] A study of 59 postoperative adolescents (12–16 years old) used doses from 0.25–1.65 mcg/kg/hr and found the lowest effective dose was 1 mcg/kg/hr.[24] Another report in 18 sickle cell patients (8–18 years old) used 0.25 mcg/kg/hr or 1 mcg/kg/hr and found no adverse effects or loss of a pain control.[25]

Treatment: A retrospective study of children 3–20 years old administered 2 mcg/kg/hr initially, titrating by 0.5 mcg/kg/hr every few hours if pruritus continues. Doses ≥3 mcg/kg/hr may increase risk of loss of pain control.[26]

Tetrahydrozoline intoxication: A neonate who was accidentally administered tetrahydrozoline nasal drops PO developed apnea and bradycardia but responded to one 0.1 mg/kg dose of naloxone.[27]

Dosage adjustment in organ dysfunction

Although one reference notes that no adjustment is needed in renal dysfunction,[28] the manufacturer recommends that naloxone be use with caution when renal or hepatic dysfunction is present.[3]

Maximum dosage

Not established.[3] 0.4 mg/kg in neonates[29] or 2 mg/dose in those >5 years or weighing >20 kg.[3,5,10,13] If no response is seen after 10-mg total dose, diagnosis of opioid toxicity is questionable.

The following doses were given without evidence of toxicity: an 8-day-old received 0.45 mg/kg/hr for 2 hours[14]; a total of 0.8 mg/kg was given in 27 hours to a 1-month-old[17]; a continuous infusion of 0.16 mg/kg/hr was given to infants for 5 days[15]; a 4½-year-old received 11 doses of 0.2 mg (2.2 mg) and a 2½-year-old was accidentally given 20 mg[3]; a 13-year-old required a cumulative dose of 0.65 mg/kg over 65.6 hours[30]; and a 17-year-old received 0.8 mg/hr for 15.5 hours.[31]

Additives

Some products contain methylparabens or propylparabens.[3] (See Appendix C for specific information about parabens potential for toxicity.)

Suitable diluents

D5W or NS.[32]

Maximum concentration

1 mg/mL for IV push.[3,32] 4 mcg/mL for continuous infusion.[3,32] Use of the concentration of 0.02 mg/mL is no longer recommended, especially in neonates, because it requires unacceptably large fluid volumes. A solution of 0.8 mg/mL has been infused in an infant.[14]

Naloxone HCl

Preparation and delivery	**Stability:** Diluted solutions should be used within 24 hours.[3] **Compatibility:** Do not mix with alkaline solutions or medications.[32] **Photosensitivity:** Should protect from excessive light.[32]
IV push	0.4 or 1 mg/mL undiluted over 30 seconds.[32]
Intermittent infusion	Not given by this method.
Continuous infusion	2 mg in 500 mL (4 mcg/mL) in D5W or NS for continuous infusion.[3,32] A solution of 8 mcg/mL has been infused in an infant.[12]
Other routes of administration	SC, IM, and ET.[3,5] The American Academy of Pediatrics does not recommend IM or SC administration due to erratic absorption but does suggest ET administration is acceptable.[10] When used, the ET dose is 2–3 times that for opiate intoxication/dependency and should be followed by an NS flush of 5 mL and five ventilations.[5] It can also be given intraosseously.[5]
Comments	**Rare adverse effects:** Two adolescents developed acute pulmonary edema postoperatively after receiving 0.1 mg and 0.5 mg (200 IV and 300 mg IM) of naloxone, respectively.[33] The pathogenesis of pulmonary edema is thought to be similar to neurogenic pulmonary edema.[3] In this condition, centrally-mediated massive catecholamine response causes a dramatic shift of blood volume into the pulmonary vascular bed producing an increased hydrostatic pressures. Hypotension/hypertension, ventricular tachycardia/fibrillation, and cardiac arrest have occurred in patients given naloxone for reversal of postoperative opioid depression.[3] Naloxone should be used cautiously in patients with pre-existing cardiac disease and in those receiving medications known to cause cardiovascular effects.[3] **Other:** Signs and symptoms of withdrawal in those who are physically dependent on opioids may include, body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure.[3] Neonates may also display seizures, excessive crying, and hyperactive reflexes.[3]

Nesiritide

Brand names	Natrecor
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that nesiritide has been confused with Nipride. USP reports that Natrecor has been confused with Primacor. USP also reports that patient death resulted when Natrecor was confused with Norcuron.[2]
Contraindications and warnings	**Contraindications:** Patients with hypersensitivity to the drug or any of its components; patients in cardiogenic shock or with systolic blood pressure <100 mm Hg.[3] **Warnings:** The potential for allergic reactions, worsening of renal function and hypotension exists. (See Significant Adverse Effects in the Comments section). Use caution in patients with a previous hypersensitivity reaction to recombinant peptides. Avoid use in patients with known or suspected low cardiac filling pressures or if cardiac output is dependent on venous return.[3]
Infusion-related cautions	Because hypotension is a dose-limiting adverse effect that may be prolonged, nesiritide should not be titrated at frequent intervals as is done with other medications that have a short half-life.[3] (See Significant Adverse Effects in the Comments section.) Nesiritide is an *E. coli*–derived product; therefore, appropriate precautions should be taken during infusions in case of allergic reactions.[3]
Dosage	Per the manufacturer, safety and effectiveness in pediatric patients have not been established.[3] **Congestive heart failure:** An IV bolus of 1–2 mcg/kg followed by a continuous infusion of 0.01 mcg/kg/min.[3–11] Increases in continuous infusion rates by 0.005 mcg/kg/min are recommended at 3-hour intervals to a maximum of 0.03 mcg/kg/min.[3–11] Infusions of up to 0.09 mcg/kg/min have been reported in children on extracorporeal membrane oxygenation (ECMO).[12] Higher dosing requirements in patients on ECMO may be related to the drug's incompatibility with heparin. **Pulmonary hypertension:** Limited success reported in children with pulmonary hypertension following cardiac repair. Intermittent infusion up to 0.2 mcg/kg/min for 15 minutes has been given directly into the pulmonary artery in a research setting.[13] **Septic shock/trauma:** Variable results reported following infusions of 0.01–0.04 mcg/kg/min.[14,15]
Dosage adjustment in organ dysfunction	No dose adjustment is recommended for renal[3] or hepatic insufficiency.[4]
Maximum dosage	The maximum recommended dose by the manufacturer is 0.03 mcg/kg/min.[3] Reports of up to 0.09 mcg/kg/min in a pediatric ECMO patient treated for hypertension[12]; however, larger dosing requirements may be due to the drug's incompatibility with heparin in the ECMO circuit. Limited experience exists for use greater than 96 hours[3]; however, it has been given for up to 45 days in a patient awaiting heart transplantation.[7]
Additives	Does not contain an antimicrobial preservative.[3]

Nesiritide

Suitable diluents	D5W, NS, D5½NS, D5¼NS.[3]
Maximum concentration	6 mcg/mL.[3]
Preparation and delivery	**Preparation:** Reconstitute nesiritide using 5 mL of suitable diluent; rock gently until solution is clear and colorless; add drug to 250-mL plastic infusion container to make a solution of 6 mcg/mL; invert several times to ensure adequate mixing.[3] **Compatibility:** Although information on infusion compatibility is limited, known incompatibilities include heparin, bumetanide, enalaprilat, ethacrynic acid, furosemide, hydralazine, and insulin.[3] Sodium metabisulfite is incompatible with nesiritide; thus, injectable drugs or solutions containing sodium metabisulfite as a preservative should not be co-infused with nesiritide.[3] **Delivery:** Prime IV tubing with 5 mL of drug solution prior to initial bolus dose or initiation of the infusion. Due to its incompatibility with heparin, infusion through a heparin-coated catheter is not recommended.[3]
IV push	Loading doses of 1–2 mcg/kg should be administered over 60 seconds.[3] Bolus dosing may not be appropriate in patients with systolic blood pressure <110 mm Hg or those recently treated with afterload reducers (i.e., nitroglycerin).[3]
Intermittent infusion	Not recommended.[3,16]
Continuous infusion	Recommended administration method.[3]
Other routes of administration	Not indicated.
Comments	**Significant adverse effects:** Concerns regarding increasing SCr in *adults* given the recommended infusion rates prompted an FDA MedWatch to alert practitioners of its potential effects on renal function.[16] It is unclear whether increases in SCr reflect hemodynamic effects or renal effects.[4,16] A recent report indicated the successful management of heart failure in a term infant with polycystic kidney disease without worsening of renal function.[17] Additionally, concerns for increased mortality rates in *adults* receiving nesiritide have prompted further investigation into its impact on survival of patients with congestive heart failure.[16] In hospitalized children with acute decompensated heart failure, continuous infusions of dopamine or nesiritide were associated with worsening renal failure.[18] Hypotension is the dose-limiting adverse effect of nesiritide. Some pediatric intensivists recommend that the bolus dose be eliminated and that therapy begin with a continuous infusion at the recommended dose rate.[7,12] Others continue to recommend bolus dose.[6,9,10] When it occurs, hypotension may be prolonged (mean 2.2 hours); therefore, observation for a prolonged period of time may be necessary.[3] Dose reductions, discontinuation of therapy, and/or supportive measures may be required.[3] Premature ventricular contractions have been reported in children with congestive heart failure.[6] **Other:** An overdose of 36 mcg/kg was reported in a child with decompensated heart failure resulting in no hemodynamic change, renal function, and/or changes in inotropic and/or vasopressor support.[7] The patient later underwent successful heart transplantation and developed no untoward long-term effects. Nesiritide has been found to improve hemodynamics in children with dilated cardiomyopathy.[19] **Monitoring:** Blood pressure and SCr should be monitored closely.[3]

NiCARdipine

Brand names	Cardene
Medication error potential	Look-alike, sound-alike drug names. NiCARdipine has been confused with NIFEdipine; no patient harm resulted.[1,2] However, niCARdipine confusion with nimodipine and nitroprusside has resulted in patient harm resulted.[2] Although Cardene has been confused with Cardizem, Cordarone, and NIFEdipine, no patient harm resulted.[2]
Contraindications and warnings	**Contraindications:** Do not use in patients with hypersensitivity to niCARdipine.[3] Contraindicated in patients with advanced aortic stenosis.[3] **Warnings:** Use caution when administering niCARdipine, particularly in combination with beta-blocker therapy, in patients with heart failure, or significant left ventricular dysfunction.[3] (See Dosage Adjustment in Organ Dysfunction section.) Also use caution when administering niCARdipine to patients with pheochromocytoma.[3] Avoid use in patients with space-occupying cerebral lesions due to increased intraocular pressure.[4]
Infusion-related cautions	If administered via peripheral line, change sites q 12 hr to avoid venous irritation/thrombophlebitis.[3,5]
Dosage	**Hypertensive emergency/severe hypertension, hypertension on extracorporeal membrane oxygenation (ECMO), during or postsurgery, and hypertension related to renal disease or postcoarctectomy** **Neonates (preterm)**[6,7] **Initial:** 0.5 mcg/kg/min. **Maintenance:** 0.5–2 mcg/kg/min; titrate q 15–30 min until target blood pressure is achieved. Has been given for up to 36–43 days. **Neonates (term) and infants** **Initial:** 0.5–1 mcg/kg/min.[8,9] **Maintenance:** 1.5–3 mcg/kg/min[8,10]; titrate q 15–30 min until target blood pressure is achieved. **Children 1–17 years** **Initial:** 1–5 mcg/kg/min[4,8,9,11–16]; some patients have received an initial dose of 10 mcg/kg/min.[11,13] **Maintenance:** Typically 2–3 (range 1–6) mcg/kg/min; titrate q 15–30 min until target blood pressure is achieved.[4,9,11–15,17–22] In hypertensive emergencies, blood pressure should be frequently monitored to ensure that it does not decrease too quickly.[23,24] One group recommended that the blood pressure decrease by one-third of the desired total blood pressure decrease within 6 hours, a further one-third decrease within the next 24–36 hours, with the final one-third decrease achieved over the next 48–72 hours.[18] Alternatively, a blood pressure decrease of <25% within minutes to 1 hour followed by further decreases over the next 2–6 hours if the patient is stable has been suggested.[25]

Dosage adjustment in organ dysfunction	No dose adjustment is recommended for renal impairment; however, conservative doses are recommended since patients with renal insufficiency may respond to lower doses or accumulate drug.[19,26] Since niCARdipine is extensively metabolized by the liver, plasma concentrations will be elevated and half-life prolonged in those with hepatic failure; therefore, dose adjustment is warranted.[3,19] Two case reports suggest that dosage changes are not required in patients supported by ECMO.[10,14] While one reference suggests that niCARdipine may be used in children with cardiac disease,[27] the manufacturer recommends caution when administering niCARdipine to patients with heart failure or significant left ventricular dysfunction due to a potential negative inotropic effect.[3]
Maximum dosage	**Initial:** 10 mcg/kg/min.[11,13] **Maintenance:** 6 mcg/kg/min.[21]
Additives	None reported.
Suitable diluents	D5W, D5NS, D5½NS, D5W with 40 mEq/L potassium, NS, ½NS.[5]
Maximum concentration	0.1 mg/mL.[3] A concentration of 3.6 mg/mL has been infused safely via a central line.[15]
Preparation and delivery	**Stability:** Product is normally a clear, yellow solution that should be stored at room temperature. Freezing does not adversely affect the product, but elevated temperatures should be avoided. NiCARdipine is not compatible with sodium bicarbonate or LR.[3,5] **Delivery system issues:** NiCARdipine (Dupont Merck) 50 and 500 mg/L in a variety of infusion solutions in PVC containers showed a decline in concentrations with nearly 50% lost in 24 hours.[5] The drug concentrations were stable when prepared in glass containers.[5] **Comptability:** NiCARdipine is not compatible with sodium bicarbonate or LR.[3,5] **Photosensitivity:** Protected from light. Deliberate exposure of a solution of 0.1 mg/mL to daylight resulted in about 8% loss in 7 hours and 21% in 14 hours.[5]
IV push	Not recommended.[3,5]
Intermittent infusion	Not recommended.[3,5]
Continuous infusion	10 mL of niCARdipine (25 mg) must be diluted before infusion by adding to 240 mL of suitable diluent to achieve a final concentration of 0.1 mg/mL. Titrate to desired effect.[3,5] More concentrated solutions (0.5 mg/mL) have been used in volume-restricted patients,[9,12,15] but thrombophlebitis has occurred.[12,15] A concentration of 3.6 mg/mL has been infused safely via a central line.[15]
Other routes of administration	No information available to support administration by other routes.

NiCARdipine

Comments

Significant adverse effects: May cause tachycardia,[11,18,19] which has been treated with propranolol.[11]

One report describes the sudden drop in blood pressure in two of four severely asphyxiated term neonates; hence, it should be used cautiously in asphyxiated patients and blood pressure should be carefully monitored.[28]

Drug interactions: NiCARdipine may be associated with drug interactions, including cyclosporine (increased cyclosporine concentrations), beta-blockers, cimetidine, and fentanyl.[3] Consult appropriate resources for dosing recommendations before combining any drug with niCARdipine.

Other: An accidental niCARdipine overdose in a pregnant patient resulted in no serious maternal or neonatal consequence.[29]

Nitroglycerin

Brand names	Generic
Medication error potential	Look-alike, sound-alike drug names. USP reports that nitroglycerin has been confused with Neo-Synephrine, nicotine, nitrofurantoin, nitroprusside, and nystatin. Nitro-Bid has been confused with Macrobid and Nitro-Dur. Tridil has been confused with Toradol.[1]
Contraindications and warnings	**Contraindications:** Patients allergic to nitrates, and in patients with pericardial tamponade, restrictive cardiomyopathy, or constrictive pericarditis.[2–4] **Warnings:** Use in patients taking sildenafil may result in severe hypotension.[2–4] **Caution:** Many different IV preparations are available for nitroglycerin; attention should be paid to the dilution and dosage when switching from one product to another.[2–4] The amount of nitroglycerin delivered is highly dependent on the type of container and administration set used.[2–4] (See Preparation and Delivery section.)
Infusion-related cautions	Severe hypotension and shock can occur with small doses. Monitor blood pressure and heart rate closely.[2–4]
Dosage	Early published studies may have used PVC administration sets, and, therefore, required doses may be reduced when low-adsorbing infusion sets are used.[2–5] **Neonates, infants, and children:** 0.1–1 mcg/kg/min, increase by 0.5–1 mcg/kg/min q 3–5 min until desired clinical response,[5–7] usually ≤20 mcg/kg/min.[8] The PALS recommendation is to begin with 0.25–0.5 mcg/kg/min and increase by 1 mcg/kg/min q 15–20 min PRN up to 1–5 mcg/kg/min (maximum 10 mcg/kg/min).[9] **Adolescents and *adults*:** 5 mcg/min, increase by 5 mcg/min q 3–5 min. When partial response is observed, use more cautious dose titration. If the desired response is not achieved at 20 mcg/min, increase by 10 mcg/min and later by 20 mcg/min until desired clinical response.[2–4] Responses are usually noted with infusion rates from 5–100 mcg/min.[10] The PALS recommendation is to begin with 5–10 mcg/min and increase to a maximum of 200 mcg/min.[9] In hypersensitive emergencies, blood pressure should be frequently monitored to ensure that it does not decrease too quickly.[10] One group recommended that the blood pressure decrease by one-third of the desired total blood pressure reduction within 6 hours, a further one-third decrease within the next 24–36 hours, with the final one-third decrease achieved over the next 48–72 hours.[11] A blood pressure decrease of <25% within minutes to 1 hour followed by further decreases over the next 2–6 hours if the patient is stable has been suggested.[10] (See Infusion-Related Cautions section.)
Dosage adjustment in organ dysfunction	No dosage adjustment required for renal dysfunction.[12]
Maximum dosage	60 mcg/kg/min was infused for ≤30 minutes to infants and children with congenital heart defects who had a low cardiac index postoperatively; however, the type of tubing used for the infusion was not stated.[6] (See Preparation/Delivery in the Preparation and Delivery section.) In *adults* with hypertension, doses up to 100 mcg/min have been used.[10] In *adults* with acute myocardial infarction, despite no absolute maximum dose, the risk of hypotension increases with doses approaching 200 mcg/min.[10] Doses of 400 mcg/min have been reported.[13] PALS recommendations include maximum doses of 10 mcg/kg/min in children and 200 mcg/min in adolescents.[9]

Nitroglycerin

Additives	One commercially available form of nitroglycerin injection contains 30% ethanol and 30% propylene glycol in water.[4] Another available form is in a solution of 50% dehydrated alcohol and 50% propylene glycol.[2] Nitroglycerin in 5% dextrose injection may contain varying additives by manufacturer including propylene glycol[3] and alcohol.[14] See Appendix C for more specific information about potential adverse effects of propylene glycol.
Suitable diluents	D5W, NS,[2–4,15] D5LR, D5½NS, D5NS, LR, ½NS.[15]
Maximum concentration	400 mcg/mL.[2–4,14,15]
Preparation and delivery	**Preparation/delivery:** Nitroglycerin readily adsorbs to many plastics; therefore, glass infusion bottles and non-PVC administration (i.e., polyolefin) sets are recommended.[2–4,14,15] Caution with nonadsorbing, high-density polyethylene plastic administration sets as over-infusion may occur.[15] If PVC sets are used, larger doses are required.[2,4,15] Avoid filters, some of which absorb nitroglycerin.[2,4,15] **Compatibility:** For PN compatibility information, please see Appendix D.
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	50–400 mcg/mL.[2–4,13,15]
Other routes of administration	IO.[9]
Comments	**Significant adverse effects:** Methemoglobinemia was associated with doses >7 mcg/kg/min in *adults*.[16,17] However, methemoglobinemia did not occur in 16 pediatric patients (3 days to 23.7 months) who received concomitant IV nitroglycerin (0.5–4 mcg/kg/min) and sodium nitroprusside (0.3–8.4 mcg/kg/min) for 0.5–7.6 days.[18] **Pharmacodynamic considerations:** In *adults*, tolerance to hemodynamic effects of nitroglycerin is observed within 12–48 hours after beginning continuous infusion. If such tolerance occurs, intermittent therapy or a nitrate-free interval ≥8 hours after 12–48 hours of continuous infusion has been recommended.[19] **Monitoring:** Blood pressure,[2–4,9] heart rate,[2–4] and ECG should be continuously monitored.[9]

Norepinephrine Bitartrate

Brand names	Levophed, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that norepinephrine has been confused with EPINEPHrine and nitroprusside. Norepinephrine has been confused with Neo-Synephrine and phenylephrine and patient harm occurred. Levophed has been confused with Lopressor, and patient harm did not occur.[2]
Contraindications and warnings	**U.S. boxed warning:** Extravasation may cause local ischemia and tissue necrosis. Aliquots of phentolamine mesylate (0.1–0.2 mg/kg up to 10 mg in 10–15 mL NS) should be injected using a fine hypodermic needle into the ischemic area. This should be done as soon as possible and within the first 12 hours of noting the extravasation.[3,4] (See Infusion-Related Cautions section.) **Contraindications:** Norepinephrine should only be used in emergency situations prior to volume resuscitation. If used in hypotensive and volume-depleted patients prior to volume replacement, peripheral and visceral vasoconstriction, decreased renal perfusion and urine output, decreased systemic blood flow, tissue hypoxia, and lactic acidosis may occur.[3,4] Do not use in patients with mesenteric or peripheral vascular thrombosis or in patients receiving cyclopropane and halothane anesthetics.[3,4] Ventricular arrhythmias may result in patients with severe hypoxia or hypercarbia.[3,4] **Warnings:** Use with caution in patients receiving monoamine oxidase (MAO) inhibitors or triptyline or imipramine antidepressants.[3,4] (See Comments section.)
Infusion-related cautions	If possible, infuse via a central,[5,6] large vein, particularly antecubital or femoral vein, using a plastic catheter inserted deep into the vein, to decrease the risk of necrosis of overlying skin.[3,4] See U.S. Boxed Warning in the Contraindications and Warnings section for extravasation antidote information. See Appendix E for additional information regarding extravasation treatment.
Dosage	Correct intravascular volume depletion prior to starting norepinephrine.[4] **Infants and children:** 0.05–0.1 mcg/kg/min titrated to the desired blood pressure up to usual maximum dose of 2 mcg/kg/min.[5–9] 2 mcg/m^2/min has also been reported.[10] **Adolescents and *adults*:** Manufacturers recommend an initial dose of 8–12 mcg/min, which is then titrated to the desired blood pressure, usually in increments of 2–4 mcg/min,[3,4] up to 30 mcg/min.[10] Other clinicians recommend starting at 0.5–1 mcg/min.[10] Continue norepinephrine dosing until adequate blood pressure and tissue perfusion aremaintained.[9,10] Avoid abrupt withdrawal by gradually reducing the dose.[3,4]
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal dysfunction.[11]
Maximum dosage	Large doses up to 68 mg/day have been used in *adults*.[3,4]

Norepinephrine Bitartrate

Additives	Some products contain sodium metabisulfite,[3] whereas others are preservative free.[4] (See Appendix C for more specific information about potential adverse effects of sulfites.) Sodium chloride is used to adjust to isotonicity.[3]
Suitable diluents	D5W, D5NS,[3,4,12] other D5-containing solutions,[3,4] LR.[12] Dilution with dextrose-containing solutions protects against significant loss of potency from oxidation.[3,4,12] Manufacturers do not suggest dilution with NS[3,4]; however, tests suggest norepinephrine is stable in NS for 7 days.[12]
Maximum concentration	16 mcg/mL.[13,14] Manufacturer does not give an absolute maximum concentration.[3,4] Concentrations up to 42 mcg/mL have been shown to be stable in D5W.[12]
Preparation and delivery	**Delivery:** May be filtered through a 0.2-micron filter without significant norepinephrine loss.[12] **Stability/photosensitivity:** Norepinephrine is easily destroyed by iron salts, oxidants, and in alkaline solutions. Protect from light. Do not infuse if solution is pink in color, darker than slightly yellow, or if a precipitate exists.[3,4] **Compatibility:** For PN compatibility information, please see Appendix D.
IV push	Not indicated.
Intermittent infusion	Not recommended.
Continuous infusion	4–16 mcg/mL. Concentrations greater and less than 4 mcg/mL may be used dependent on the drug and fluid requirements of the individual patient.[3,4,13] The Joint Commission recommends the use of standardized concentrations of vasoactive medications.[15] The ISMP and Vermont Oxford Network recommend a standard concentration of 16 mcg/mL for neonates.[16]
Other routes of administration	IO.[7,8,17]
Comments	Several drugs (e.g., tricyclic antidepressants, MAO inhibitors) may potentiate the pressor effects of norepinephrine.[3,4] Atropine may block the reflex bradycardia and enhance the pressor response caused by norepinephrine.[10] Consult appropriate resources before combining any drug with norepinephrine. For hypotension due to tricyclic antidepressant and other sodium channel blocker toxicity, norepinephrine and EPINEPHrine have been shown to be superior to DOPamine in elevating blood pressure.[8] Norepinephrine infusion may overcome hypotension-related toxicities associated with reduced systemic vascular resistance of milrinone and inamrinone.[8] **Monitoring:** Blood pressure, ECG,[6] and central venous pressure monitoring, when possible, monitoring should occur continuously throughout therapy.[3,4]

Octreotide Acetate

Brand names	SandoSTATIN
Medication error potential	Look-alike, sound-alike drug names. Tall man letters (not FDA approved) is recommended to decrease confusion between SandoSTATIN and SandIMMUNE.[1,2] SandoSTATIN injection may be administered SC or IV; Sandostatin LAR Depot should only be given IM.[3,4]
Contraindications and warnings	**Contraindications**: Hypersensitivity to octreotide or any of its components.[3] **Warnings:** May inhibit gallbladder contraction and decrease bile secretion; gallstones, acute cholecystitis, ascending cholangitis, biliary obstruction, cholestatic hepatitis, and pancreatitis have been reported in patients receiving octreotide.[3] Hypoglycemia or hyperglycemia, suppression of thyroid-stimulating hormone resulting in hypothyroidism, and cardiac conduction abnormalities have been reported in patients receiving octreotide. These effects may be seen more frequently in patients with acromegaly.[3]
Infusion-related cautions	Case report of a 12-year-old with history of chronic pancreatitis, previously treated with octreotide (6 mcg/kg once daily). Two weeks after the initial episode, the patient developed recurrent pancreatitis and was restated on octreotide (1.3 mcg/kg/dose q 8 hr). During the administration of the tenth dose, he immediately experienced flushing, erythema, periorbital, and perioral angioedema, difficulty breathing, cough, and abdominal pain. Octreotide was stopped and pheniramine was given. His physical findings improved within 5 minutes and he was back to baseline within 1 hour. Upon re-exposure, he developed this reaction again, so a desensitization protocol was instituted for the duration of this octreotide treatment.[5]
Dosage	**Chylothorax/chyloperitoneum:** 0.3–4 mcg/kg/hr via continuous IV infusion followed by a gradual increase in dose to desired effect.[6–16] Titrations up to 6–12 mcg/kg/hr have been reported in infants and children.[12,13,15–17] 10 mcg/kg/day in 3 divided doses SC[18–20]; increase dose by 5–10 mcg/kg/day at 48- to 96-hour intervals to desired effect.[18,20] Typically titrate up to 20–40 mcg/kg/day in 3 divided doses.[18,20,21] A systematic review of 20 reports of octreotide therapy for chylothorax recommended larger doses (80–100 mcg/kg/day) earlier rather than starting with a low dose and titrating gradually upward.[22] **Diarrhea/increased GI output:** 13–200 mcg/day SC or IV in 2 divided doses.[23–28] Doses of 1.4–20 mcg/kg/day divided q 12 hr have been used.[23,24,26–28] Begin at the low end of the dosage range and increase by 0.3 mcg/kg/dose q 3 days.[23] An alternative method is continuous infusion of 1 mcg/kg/hr.[29] A recent study showed better response rate to octreotide in patients with chemotherapy-associated diarrhea (92%) compared to patients with acute graft versus host disease-associated diarrhea (45%). Mean starting dose in these patents was 4 mcg/kg/day (range: 1–23 mcg/kg/day) with a maximum dose of 9 mcg/kg/day (range: 1–49 mcg/kg/day).[30] **Fistula closure** **Neonates:** 1.4 mcg/kg/day SC divided BID, gradually increased up to 5 mcg/kg/day SC divided BID.[31] **Children:** 50–300 mcg/day SC divided in 2–3 doses. Start at lower end of dosage range and increase gradually.[32]

Dosage *(cont.)*

GI bleeding: Bolus of 1–2 mcg/kg[33] followed by IV infusion 1–2 mcg/kg/hr.[33,34] Older children have received an *adult* dose (50 mcg over 5 minutes followed by 50 mcg/hr). Continuous infusion can be increased every 8 hours if there is no decrease in bleeding. Once there is no active bleeding, the dose is tapered by 50% every 12 hours and can be stopped when the dose is 25% of initial dose.[33–35] For chronic GI bleeding, 4–8 mcg/kg/day SC has been given with concurrent iron therapy.[36]

Hyperinsulinemia (congenital)/hypoglycemia of infancy: Initial doses of 2–10 mcg/kg/day in 2–6 doses SC.[37–44] Doses are titrated up to 40 mcg/kg/day based on glucose concentrations. Total daily dose may be given SC in divided doses or continuous infusion via a SC or IV infusion pump.[28,37,40]

Pancreatitis/pancreatic tumors: A 10-year-old received somatostatin 1.5 mcg/kg/hr IV continuous infusion for pancreatic pseudocyst.[45] A 15-month-old infant received 2 mcg/kg SC q 6 hr increased up to 20 mcg/kg for recurrent acute pancreatitis and ascites.[46] A 12-year-old received a titrated dose (maximum of 75 mcg/kg/dose) of octreotide SC in combination with chemotherapy for malignant pancreatic carcinoid tumor.[47] Four patients with acute lymphoblastic leukemia (ALL) who developed asparaginase-associated pancreatitis were effectively treated with octreotide continuous IV infusion. Octreotide was initiated at 7.2 mcg/kg/day and titrated down to 3.6 mcg/kg/day for 2 days and 1.8 mcg/kg/day for 2 days once abdominal pain improved.[48] Three patients with ALL who had a history of asparaginase-associated pancreatitis were treated with octreotide once daily SC (2.5–4 mcg/kg/day) for prevention of pancreatitis after retreatment with asparaginase.[49]

Sulfonylurea poisoning: In children, a single dose of 25 mcg can be given IV. Dose and duration vary depending on amount of sulfonylurea ingested and its half-life.[50–53] Continuous infusion, SC, and IV are appropriate routes, and 2 mcg/kg/day SC divided q 12 hr has also been cited as appropriate.[50] 2 mcg/kg followed by 2 mcg/kg/hr has been used in a toddler with hypoglycemia unresponsive to dextrose infusion and glucagon.[54]

Tall stature/excessive growth hormone (GH) secretion (use not established): 100–500 mcg 2–3 times daily up to 1500 mcg/day has been used but has not fully suppressed GH levels.[28,55]

Children: 300–600 mcg/day in 3 divided doses.[28,55]

Adolescents: 500–1500 mcg/day in 2–3 divided doses.[28]

One study found 37.5 mcg (prepubertal) or 50 mcg (pubertal) given via SC injection 1 hour before bedtime to be effective in children.[56] Continuous SC infusion with the bulk of the total daily dose given overnight has been found to be superior to SC or depot injection therapy.[55]

Dosage adjustment in organ dysfunction

Dosage adjustment is needed for depot injection in patients with dialysis-dependent renal impairment and with established cirrhosis of the liver. In *adults*, the adjusted dose is 10 mg IM q 4 wk (50% reduction) and titrated based on response.[57]

Maximum dosage

No data for maximum dosage in children. (See Comments section.) In *adults*, the maximum dose is 1500 mcg/day divided q 8 hr.[3,57]

Additives

Sandostatin products contain lactic acid, mannitol, phenol (in multidose vials but not ampuls), and sodium bicarbonate (for pH adjustment).[3,4]

The Bedford formulation contains lactic acid, sodium chloride and sodium hydroxide (for pH adjustment), and phenol (multidose vial).[4]

Suitable diluents

D5W,[3,57] NS.[3,4]

Maximum concentration

In emergency situations, octreotide may be administered undiluted.[3]

Octreotide Acetate

Preparation and delivery	**Stability:** Should be stored under refrigeration. Allow solution to come to room temperature before administration. Can be stored at room temperature for up to 14 days when protected from light.[4] **Compatibility:** The manufacturer states that octreotide should not be added to PN because of the formation of glycosyl octreotide conjugate[3]; however, this is controversial.[4] **Photosensitivity:** Protect from light.[4]
IV push	In emergency situations, may be administered over 3 minutes.[3,4,57]
Intermittent infusion	Dilute with 50–200 mL and infuse over 15–30 minutes.[3,4,57]
Continuous infusion	Dilute and infuse over 24 hours.[3,4,57]
Other routes of administration	SC injection is the usual route of administration.[3] SC injection sites should be rotated.[3] Use the concentration with the smallest volume to reduce injection site pain. Allow solution to come to room temperature prior to injection.[57] IM administration with depot form only (Sandostatin LAR Depot).[3,4] Reconstitute with provided diluent and administer immediately after reconstitution into gluteal area (avoid deltoid injections due to pain and discomfort at injection site).[57]
Comments	**Significant adverse effects:** A systematic review of somatostatin or octreotide in infants and young children reported side effects of cutaneous flush, nausea, loose stools, transient hypothyroidism, elevated liver function tests, strangulation ileus (with somatostatin) and transient abdominal distention, temporary hyperglycemia, and necrotizing enterocolitis (NEC) (with octreotide).[6] Severe paradoxical hyperglycemia and bradycardia has been reported in an infant receiving octreotide 0.5 mcg q 6 hr SC during subtotal pancreatectomy for congenital hyperinsulinism.[58] A 6-month-old infant died of fulminant colitis after receiving somatostatin analogue in a dose of 18 mcg/kg/day. Prior to the infant's death, the dose had been decreased to 3.5 mcg/kg/day.[59] A 16-month-old with enterocutaneous fistula developed sudden abdominal pain and increased nasogastric drainage and died 8 hours after receiving a single dose of 100 mcg SC of somatostatin analogue.[3] Several reports in neonates and infants have associated the use of octreotide to the development of NEC.[8,60,61] Asymptomatic gallstones were found in an infant 1 year after being started on octreotide.[37] **Other:** Tachyphylaxis is a common occurrence, requiring larger doses to maintain similar effect, especially when used in patients with hyperinsulinism.[38,40,41] Octreotide has been used to improve GI symptoms (abdominal pain, nausea, vomiting) in a 12-year-old with bowel obstruction due to progression of adenocarcinoma despite surgery and chemotherapy.[62] May decrease vitamin B_{12} concentrations and alter dietary fat absorption.[3] Fat malabsorption documented by fecal fat testing was observed in one infant on prolonged octreotide therapy.[44]

Ondansetron HCl

Brand names	Zofran
Medication error potential	Look-alike, sound-alike drug names. USP reports that ondansetron has been confused with dolasetron, granisetron, and olanzapine.[1] No patient harm occurred. Zofran was confused with Reglan, Zantac, Zocor, Zoloft, Zometa, and Zosyn and no patient harm resulted. However, Zofran was confused with Zanaflex and patient harm did occur.
Contraindications and warnings	**Contraindications:** Patients with known hypersensitivity to the drug.[2] Concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness.[2] **Warnings:** Hypersensitivity reactions may occur in patients with hypersensitivity to other 5-hydroxytryptamine 3 (5-HT3) antagonists.[2] An anaphylactoid reaction occurred in an 11-year-old girl.[3] Postmarketing cases of torsades de pointes have been reported. Avoid use of ondansetron in patients with congenital long QT syndrome. Use ECG monitoring in patients with hypokalemia, hypomagnesemia, congestive heart failure, bradyarrhythmias, or patients receiving medications that lead to QT prolongation.[2]
Infusion-related cautions	Blood pressure changes and increased QTc interval have been reported during infusion in *adults*.[4]
Dosage	**Prevention of chemotherapy-induced nausea and vomiting:** 0.15 mg/kg over 15 minutes given 30 minutes before chemotherapy with 2 or 3 additional doses given 4 and 8 hours after the first dose.[2,5–10] A single dose of 0.6 mg/kg (≤32 mg/dose) was no more effective than 0.15 mg/kg (≤8 mg) q 4 hr for 4 doses.[9] Similarly, no difference in efficacy was noted between 5 (≤8 mg) and 10 mg/m^2 (≤16 mg).[11] The inclusion of dexamethasone is recommended.[12] In 26 children (18 months to 15 years) undergoing IT chemotherapy who received 0.45 mg/kg given 30 minutes prior to treatment, vomiting was decreased compared to those who received 0.15 mg/kg.[11] In *adults*, 3 doses of 0.15 mg/kg up to a maximum of 16 mg/dose. First dose should be infused 15–30 minutes prior to the start of emetogenic chemotherapy, followed by subsequent doses at 4 and 8 hours after the first ondansetron dose.[2,6] Use of single doses of 32 mg is no longer recommended.[2] **Prevention of postoperative nausea and vomiting (PONV):** ≥1 month old to ≤40 kg: 0.1 mg/kg given once.[2,14] >40 kg to 12 years of age: ≤4 mg given once.[2,14] Others report infusing 0.025–0.15 mg/kg immediately before or immediately after induction of anesthesia or postoperatively in symptomatic patients.[15–23] One study noted that 0.075 mg/kg was as effective as 0.1–0.15 mg/kg.[21] Administration of a second dose in patients who fail to respond does not improve control.[2] **ED treatment of acute gastroenteritis:** 0.15 mg/kg, infused over 2 minutes in children 1 month to 22 years, reduced the need for hospital admission and decreased the number of vomiting episodes in the acute period of illness.[24,25]
Dosage adjustment in organ dysfunction	No dosage adjustment for renal noted.[2] In patients with severe hepatic impairment, administer a single dose (maximum 8 mg) infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy.[2]
Maximum dosage	0.45 mg/kg[13] up to 16 mg/dose.[2] In *adults*, up to 150 mg/dose and up to 252 mg/day have been inadvertently given without adverse effects.[2]

Ondansetron HCl

Additives	Each mL of the 20-mL multidose vial contains 8.3 mg of sodium chloride, 0.5 mg of citric acid monohydrate, 0.25 mg of citrate dihydrate, 1.2 mg of methylparaben, and 0.15 mg of propylparaben.[2,26] Each mL of the single dose vial contains 9 mg of sodium chloride, 0.5 mg of citric acid monohydrate, and 0.25 mg of sodium citrate dihydrate.[2,25] (See Appendix C for specific information about potential adverse effects.)
Suitable diluents	D5W, D5 ½NS, D5NS, LR, NS, R.[2,26]
Maximum concentration	2 mg/mL (undiluted) for PONV prophylaxis.[2] Dilute for prevention of chemotherapy-induced nausea and vomiting.[2]
Preparation and delivery	**Stability:** Must be used within 24 hours of dilution.[2] **Compatibility:** See Appendix D for PN compatibility information.
IV push	In children <40 kg receiving 0.1 mg/kg and those >40 kg (including *adults*) receiving 4 mg for prevention of PONV, ondansetron may be infused over >30 seconds but over 2–5 minutes is preferable.[2]
Intermittent infusion	Infuse over 15 minutes for prevention of chemotherapy-induced nausea and vomiting.[2,7]
Continuous infusion	Although continuous infusion has been used in *adults*,[27] its use has not been reported for pediatric patients.
Other routes of administration	Can be given IM in *adults*.
Comments	**Pharmacokinetics:** Compared to those 4–12 months old, infants 1–4 months have decreased clearance resulting in a prolonged half-life.[2] Those <4 months old should be closely monitored.[2] Children and adolescents have increased clearance and shorter half-life than *adults*.[2] **Drug interactions:** Ondansetron is metabolized by the cytochrome P450 isozymes, but neither induces or inhibits the isozymes. While ondansetron clearance is increased and concentrations are decreased by rifampin, carbamazepine, and rifampicin, no dosage adjustment for ondansetron is recommended.[2] Profound hypotension and loss of consciousness have been reported when apomorphine was administered with ondansetron.[2] **Adverse events:** Blurred vision has been noted. Transient blindness has been reported and resolves within a few minutes up to 48 hours.[2]

Oxacillin Sodium

Brand names

Generic

Medication error potential

Look-alike, sound-alike drug names.

USP reports confusion with ampicillin, cefazolin, nafcillin, and penicillin G potassium.[1]

Contraindications and warnings

Contraindications: Hypersensitivity to oxacillin or other penicillins or any component of the formulation.[2]

Warnings: Individuals who have a type I reaction to penicillin may experience serious and occasionally fatal hypersensitivity (anaphylactic shock with collapse) reactions.[2] (See Appendix C for specific information.)

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]

Infusion-related cautions

If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.[2]

Dosage

Neonates

PNA	≤1200 g	≤2000 g	>2000 g
≤7 days	50 mg/kg/day divided q 12 hr[3,4]*	50–100 mg/kg/day divided q 12 hr[3,4]	75–150 mg/kg/day divided q 8 hr[3]
>7 days		75–150 mg/kg/day divided q 8 hr[3]	100–200 mg/kg/day divided q 6 hr[3]

*Until 4 weeks of age.

Infants and children

Mild-to-moderate infections: 50–150 mg/kg/day divided q 6 hr (up to 4 g/day).[2,3]

Severe infections: 100–200 mg/kg/day divided q 4–6 hr (up to 12 g/day).[2,3]

Dosage adjustment in organ dysfunction

Although no specific recommendations are made, the manufacturer recommends altering the dose in renal dysfunction.[2]

Maximum dosage

≤12 g/day for those with severe infections in *adults*.[5] Although doses of 400 mg/kg/day have been given, they have been associated with hepatotoxicity.[6]

Additives

Contains 2.5–3.1 mEq sodium/g of oxacillin.[2]

Suitable diluents

D5W, D10W, NS, ½NS, LR, SW, D5NS, D5LR.[7] Specific references should be used as stability over time was variable in these diluents.[7]

Maximum concentration

100 mg/mL for IV push.[2]

Oxacillin Sodium

Preparation and delivery	**Delivery system issues:** The mixing of penicillins with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[2] (See Appendix C for more specific information.) **Compatibility:** See Appendix D for PN compatibility information.[8]
IV push	100 mg/mL over at least 10 minutes.[2,7]
Intermittent infusion	0.5–40 mg/mL.[2,7] If given peripherally, consider infusing over 60 minutes at a maximum concentration of 20 mg/mL.[9] Up to 106 mg/mL in SW has been recommended for fluid restricted patients.[7]
Continuous infusion	Oxacillin has been given by this method to *adults*.[10,11]
Other routes of administration	167 mg/mL in SW,[2] NS, or ½NS may be given by deep IM injection in same doses as IV.[7]
Comments	**Rare adverse effects:** Hepatotoxicity, characterized by fever, nausea, and vomiting associated with abnormal liver function tests, mainly elevated aspartate aminotransferase (AST) levels, has been associated with the use of oxacillin.[12,13] Cholestatic hepatitis has been reported rarely. Neurotoxic (e.g., lethargy, confusion, twitching, multifocal myoclonus, localized or generalized epileptiform seizures) may occur with large doses, especially in patients with renal insufficiency.[2,14] **Monitoring:** AST and alanine aminotransferase (ALT) values should be obtained periodically during therapy to monitor for possible liver function abnormalities.[2] **Drug interactions:** Concurrent use of tetracycline should be avoided as it may antagonize the bactericidal effect of penicillin.[2] Probenecid may decrease the tubular secretion of oxacillin and increase its concentration in the serum.[2] Consult appropriate resources for dosing recommendations before combining any drug with oxacillin.

Palivizumab

Brand names	Synagis
Medication error potential	None noted.
Contraindications and warnings	**Contraindications:** Those with a previous hypersensitivity reaction to palivizumab.[1] **Warnings:** Rare cases of acute hypersensitivity reactions or anaphylaxis have been reported after re-exposure to palivizumab.[1] If milder hypersensitivity reactions occur with palivizumab, subsequent doses should be given with caution.
Infusion-related cautions	Not given by IV infusion.
Dosage	**Indications:** Infants born at ≤35 weeks gestational age (WGA) or who have bronchopulmonary dysplasia and infants who have stable hemodynamically significant (cyanotic or acyanotic) congenital heart disease (CHD).[1] Dosing should begin prior to the anticipated respiratory syncytial virus (RSV) season.[1] 15 mg/kg IM in the anterolateral aspect of the thigh repeated q 30 days during the RSV season for up to 5 doses.[1–9] Most infants and children who require palivizumab are treated as outpatients. However, it has been used in hospitalized preterm infants who met eligibility criteria during outbreaks.[10,11] In general, AAP recommends prophylaxis for[12] **Up to 5 doses** Infants and children <24 months of age with chronic lung disease (CLD) who require medical treatment for CLD. Infants and children <24 months of age with CHD who require medical treatment for CHD. Infants born ≤32 WGA. Certain infants with neuromuscular disease or congenital malformation of the airways. **Up to 3 doses** Infants with a 32–35 WGA with at least one risk factor for hospitalization and born no more than 3 months before RSV season.
Dosage adjustment in organ dysfunction	None noted.
Maximum dosage	15 mg/kg monthly.[1]
Additives	Contains no preservatives.
Suitable diluents	Should not be diluted.[1]
Maximum concentration	100 mg/mL for IM use.[1]

Palivizumab

Preparation and delivery	Do not shake or agitate the vial.[1] 50- and 100-mg vials are single dose.[1] Do not re-enter the vial.[1]
IV push	The manufacturer does not recommend IV infusion. However, palivizumab was infused over 2–5 minutes or 1–2 mL/min (10 mg/mL) in pharmacokinetic studies[13,14] and in infants with RSV infection who were mechanically ventilated.[15]
Intermittent infusion	Not indicated.
Continuous infusion	Not indicated.
Other routes of administration	IM is the usual route of administration. If the dosage volume exceeds 1 mL, the dose should be divided and given as separate injections.[1] Use of the combination of EMLA cream and 50/50 nitrous oxide/oxygen significantly decreased pain associated with injection than either used alone.[16]
Comments	Administration of palivizumab IV to patients in the acute phase of RSV illness did not improve clinical outcomes nor cause an exacerbation of the infection[14]; however, concentrations of virus in tracheal aspirates were reduced when administered at standard prophylactic doses.[15] Serum concentrations decreased by a mean of 58% following cardiopulmonary bypass in pediatric patients receiving open heart surgery, thus additional dosing after surgery may be required.[1] Lower doses (3–10 mg/kg) were associated with insufficient serum antibody concentrations.[6,13]

Pamidronate

Brand names	Aredia
Medication error potential	Look-alike, sound-alike drug names. USP reported the potential for confusion between pamidronate and papaverine.[1]
Contraindications and warnings	**Contraindications:** Hypersensitivity to pamidronate or other bisphosphonates.[2] **Warnings:** Pamidronate should be infused slowly over at least 2 hours to avoid renal impairment.[2]
Infusion-related cautions	Infusion site reactions are more likely to occur with larger doses.[2]
Dosage	**Osteogenesis imperfecta:** Regimens vary[3–6] but in general range from 1–1.5 mg/kg given every other month or q 3 mo.[7–9] Calcium and vitamin D supplements should be provided. Treatment may be continued for several years. Because of concerns over growth, one group discontinued treatment for 2 years and found that bone metabolism continued to be suppressed, improvements in bone mass continued, but children did not achieve normal bone growth.[10] **Osteoporosis/osteopenia:** 0.4–1 mg/kg over 2–4 hours for 3 days q 3–6 mo for up to 13 months in children with cerebral palsy.[11,12] Seventeen children on steroids for endocrine or renal disease who developed fractures were given 1 mg/kg q 2 mo for 1 or 2 years.[13] Patients were also prescribed calcium and vitamin D supplements.[12,13] Fifteen children with osteoporosis received either 1 mg/kg for one day q 3 mo or 1 mg/kg/day for 3 days q 4 mo with comparable increases in adjusted bone mineral density.[14] **Hypercalcemia:** 0.5–1 mg/kg[15–19] or 35–50 mg/m^2[20] over 2–6 hours as a single dose or repeated for 1[20] or 2 more days.[18] One group repeated the initial 0.5 mg/kg dose on days 1–3 and then decreased the dose to 0.25 mg/kg on day 4 and 0.125 mg/kg on day 5.[21] **McCune Albright syndrome:** 0.5 mg/kg over 4 hours for 3 days each year, 1 mg/kg over 4 hours for 3 days q 6 mo, or 1 mg/kg for 3 days q 4 mo for up to 6 years,[22] or 1 mg/kg over 4 hours for 3 days q 6 mo for 2 years.[23]
Dosage adjustment in organ dysfunction	None recommended by manufacturer.[2] However, in those whose renal function deteriorates during treatment, the dose should be held until renal function returns to baseline.[2] Longer infusions (>2 hours) in patients with preexisting renal insufficiency may reduce the risk of renal toxicity.[2] One report described three children with renal failure or who were postrenal transplant with either fractures or hypercalcemia who were given 1–3 doses of 0.4–0.5 mg/kg without ill effects.[24]
Maximum dosage	1.5 mg/kg q 2 mo has been used in osteogenesis imperfecta.[9] 90 mg q 3–4 wk in *adults* with metastatic bone disease.[2] Single doses should not exceed 90 mg due to renal effects.[2]
Additives	470 mg mannitol in 30-mg vials. 375 mg mannitol in 90-mg vials.[2]
Suitable diluents	D5W, ½NS, NS.[2]
Maximum concentration	0.36 mg/mL.[2]

Pamidronate

Preparation and delivery	Reconstitute 30 or 90 mg lyophilized powder in 10 mL SW. Dilute reconstitution in 250 mL to 1 L of D5W, ½NS, NS. **Compatibility:** Incompatible with calcium-containing fluids (including LR) and other parenteral drugs.[2]
IV push	Contraindicated.
Intermittent infusion	In *adults*, 30–90 mg over ≥2–4 hours. Longer infusion times decrease the risk for renal toxicity.[2]
Continuous infusion	90 mg infused over 24 hours in *adults*.[2]
Other routes of administration	Not indicated.[2]
Comments	**Monitoring:** SCr should be measured before each infusion.[2] **Adverse effects:** A transient, low-grade fever for 24–48 hours is common after the first infusion. The frequency of this reaction decreases with subsequent infusions.[2,7,8,13,15,22] Symptomatic and asymptomatic hypocalcemia has been reported.[2,3,17] Osteonecrosis of the jaw has been reported in *adult* cancer patients on chemotherapy who also receive pamidronate. It is recommended that while on pamidronate invasive dental procedures should be avoided.[2] Twenty-two children who underwent 38 dental procedures exhibited no evidence of jaw osteonecrosis.[25]

Pancuronium Bromide

Brand names	Pavulon, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that pancuronium has been confused with vecuronium; no patient harm resulted. USP also reports that pancuronium has been confused with Protonix; patient harm resulted.[2] ISMP reports that Pavulon has been confused with Peptavlon.[3] USP reports that Pavulon has been confused with papaverine; no patient harm resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** Pancuronium should be administered only by adequately trained individuals familiar with the actions, characteristics and hazards of pancuronium.[4] **Contraindications:** Hypersensitivity to pancuronium or any of its components.[4] **Other warnings:** Use carefully under the supervision of experienced clinicians; personnel should be skilled in airway management, resuscitation, and respiratory support. Intubation and ventilatory support equipment, including oxygen therapy, should be readily available. Reversal agents should be readily available when giving pancuronium.[4] Patients with myasthenia gravis or Eaton-Lambert syndrome may have profound effects and require very small doses.[4]
Infusion-related cautions	Cardiac dysrhythmias, tachycardia, and hypertension have been reported.[5–7] Joint contractures have occurred in neonates.[8] Anaphylactoid reactions have occurred in *adults*.[9]
Dosage	*Respiratory function must be supported during use of this agent. Concurrent administration of a sedative is also necessary. Monitoring of neuromuscular transmission with a peripheral nerve stimulator is recommended during continuous infusion or with repeated dosing.*[4] **Induction and maintenance of neuromuscular blockade** **Neonates:** Because neonates are particularly sensitive to nondepolarizing agents, a test dose of 0.02 mg/kg should be given to assess responsiveness.[4] 0.03–0.1 mg/kg repeated as necessary q 1–2 hr to maintain muscle relaxation.[4,10–16] For neonatal nonemergent intubations, AAP recommends that vagolytic and muscle relaxant agents should be considered, and that analgesic agents or anesthetic doses of a hypnotic agent should be administered. Pancuronium is an acceptable muscle relaxant (rocuronium or vecuronium is preferred).[17] **Infants and children:** 0.08–0.15 mg/kg initially and then 0.01–0.15 mg/kg repeated as required or 0.02–0.06 mg/kg/hr (0.4–1 mcg/kg/min) as continuous infusion.[4–6,16,18–20]
Dosage adjustment in organ dysfunction	Adjust dosage in patients with renal dysfunction.[21,22] If CrCl is 10–50 mL/min/1.73 m^2, give 50% of a normal dose; if CrCl is $<$10 mL/min/1.73 m^2, do not use.[21,22] For patients undergoing continuous renal replacement therapy (CRRT), give 50% of a normal dose and titrate to effect.[21] Although clearance is decreased, volume of distribution is significantly increased in patients with liver dysfunction; hence, these patients may require larger initial doses but have prolonged recovery times.[4,23]

Pancuronium Bromide

Maximum dosage	Cumulative dose of 0.3 mg/kg was given within several minutes to a newborn infant without adverse effects.[13] One study used up to 0.5 mg/kg as a single dose in neonates with hyaline membrane disease.[24]
Additives	**Benzyl alcohol:** Multidose vials contain benzyl alcohol 0.9% as a preservative.[4] (See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.)
Suitable diluents	D5W, D5NS, D5½NS, NS, LR.[4,25]
Maximum concentration	2 mg/mL (undiluted) for IV push or 0.8 mg/mL for continuous infusion.[4,18]
Preparation and delivery	No comments.
IV push	1 or 2 mg/mL given rapidly over seconds.[4,18]
Intermittent infusion	No information available to support administration by this method.
Continuous infusion	0.01–0.8 mg/mL.[18]
Other routes of administration	IM administration is not recommended.[4]
Comments	**Significant adverse effects:** Prolonged paralysis (mean duration of 9 weeks) has been reported following pancuronium infusion.[26–28] Factors that potentiate the duration of neuromuscular blockage include use of certain medications (see Drug Interactions below), acidosis, hyponatremia, hypocalcemia, hypokalemia, and hypermagnesemia.[4,16,18] **Drug interactions:** Concomitant administration of corticosteroids with neuromuscular blockers has been shown to be a risk factor for prolonged paralysis.[29] Likewise, concomitant administration of pancuronium with certain antibiotics (e.g., aminoglycosides) and other drugs such as anesthetics, magnesium, and quinidine may also prolong neuromuscular blockade.[16,18] Consult appropriate resources for additional information on drug interactions.

Pantoprazole

Brand names	Protonix
Medication error potential	Look-alike, sound-alike drug names. USP reports that Protonix has been confused with pancuronium.[1] USP also reports that pantoprazole has been confused with paroxetine, Pravachol, pravastatin, and propranolol, Paxil, Plavix, Pravachol, Primaxin, protamine sulfate, Proteinex, and Topamax.[1] ISMP reports that Protonix has been confused with Lotronex and protamine.[2]
Contraindications and warnings	Pantoprazole is contraindicated in patients with known hypersensitivity to the formulation.[3]
Infusion-related cautions	Immediate hypersensitivity reactions, including anaphylaxis, may occur.[3] Thrombophlebitis and injection site reactions have been reported.[3]
Dosage	Experience with IV pantoprazole in children, particularly neonates and infants, is limited; currently there is no established IV dose range for pediatric patients. Initial pharmacokinetic studies of oral and IV pantoprazole in children 2–16 years of age have found similar pharmacokinetics to that observed in *adults*.[4–6] In *adults*, oral and IV dosage are similar in potency. **Doses used in pediatric IV pharmacokinetic studies[4–6]:** 0.47–1.88 mg/kg/dose, maximum 80 mg/dose and 160 mg/day (children 2–16 years). **Dosing ranges from pediatric oral dosing studies** **Gastroesophageal reflux/reflux esophagitis** **Preterm and term neonates and infants:** 1.2 mg/kg/day for ≤6 weeks.[7,8] **Children 1 month to 6 years:** 1.2 mg/kg/day provided the same exposure as *adults* receiving 40 mg.[9] **Children 6–13 years:** 20 mg every day (0.5–1 mg/kg/day) for 28 days.[10] ***Adult* dosing ranges (IV pantoprazole)** **Gastroesophageal reflux/reflux esophagitis[3]:** 40 mg every day for 7–10 days; oral formulation for maintenance. **Hypersecretory conditions[3]:** 80 mg q 12 hr for up to 6 days; may increase frequency to q 8 hr PRN to suppress acid production.
Dosage adjustment in organ dysfunction	No dosage adjustment recommended for renal or hepatic dysfunction.[3,11] Doses >40 mg/day have not been studied in patients with hepatic dysfunction.[3] Elimination half-life may be prolonged with hepatic dysfunction.[12]
Maximum dosage	80 mg/dose[5,6] and 160 mg/day[6] in children. 240 mg/day in *adults*.[3]
Additives	Edetate disodium (1 mg per 40-mg vial).[3,13] Edetate disodium is a chelator of metals, and the manufacturer recommends that zinc supplementation should be considered in patients receiving pantoprazole who are prone to zinc deficiency.[3]
Suitable diluents	Reconstitute to 4 mg/mL with NS. Further dilution may be done with D5W, LR, NS.[3,13]

Pantoprazole

Maximum concentration	4 mg/mL.[3,13]
Preparation and delivery	**Delivery:** Administer via a dedicated line or Y-site administration after flushing the line before and after with a suitable diluent.[3] **Compatibility:** Observe for any signs of precipitation when administering via Y-site.[3]
IV push	May administer reconstituted solution of 4 mg/mL over a minimum of at least 2 minutes.[3,13]
Intermittent infusion	Dilute to 0.4–0.8 mg/mL with suitable diluent and infuse over 15 minutes at a maximum rate of 7 mL/min.[3,13]
Continuous infusion	Not recommended.[3] In *adults*, a single IV load of 80 mg followed by 8 mg/hr has been used for 3 days.[14–16]
Other routes of administration	No information available to support administration by other routes.
Comments	**Significant adverse effects:** Administration of proton pump inhibitors (PPIs) has been associated with increased risk of developing gastroenteritis and pneumonia in children.[17] Adverse effects may include mild elevation of liver function tests.[3] Prolonged use (>3 years) may lead to impaired absorption of cyanocobalamin (vitamin B_{12}) due to achlorhydria.[18] An *adult* patient developed generalized edema following the initiation of intermittent IV pantoprazole for the treatment of pyloric stenosis.[19] Peripheral edema has been more commonly reported in patients receiving PPIs via continuous infusion of large volumes. **Drug interactions:** Pantoprazole is metabolized primarily by CYP2C19 and to a lesser extent by CYP3A4. Drug interaction potential is unknown in patients with hepatic dysfunction or in those receiving large doses.[3] Consult appropriate resources for dosing recommendations before combining any drug with pantoprazole. A known interaction exists between pantoprazole and clopidogrel. Since clopidogrel is metabolized to its active metabolite primarily via CYP2C19, and to a lesser extent, via CYP3A4 and CYP2C9, its use with pantoprazole may decrease the formation of the active metabolite and decrease antiplatelet effects.[20] **Pharmacokinetic considerations:** A randomized, open-label, multicenter trial in hospitalized patients 2–16 years of age found the pharmacokinetics of single oral and IV 0.8 or 1.6 mg/kg pantoprazole doses to be similar to doses of 20, 40, or 80 mg in *adults*. The authors noted that plasma clearance in the children appears to be related to CYP2C19 genotype rather than age.[6] Another pharmacokinetic study (computer generated method) evaluated 19.9–140.6 mg/1.73 m^2/day IV pantoprazole in critically ill pediatric patients (10 days to 16.4 years of age) and found more rapid clearance in patients 6 months to 5 years compared to *adults*.[21] **Laboratory interference:** False–positive urine tetrahydrocannabinol has been reported in patients taking PPIs, including pantoprazole.[3]

Papaverine HCl

Brand names	Generic
Medication error potential	Look-alike, sound-alike drug names. USP reports that papaverine has the potential to be confused with pamidronate and has been confused with Pavulon.[1]
Contraindications and warnings	**Contraindications:** Complete atrioventricular heart block.[2] **Other Warnings:** Use caution in patients with glaucoma.[2] Use caution in very low birth weight neonates in the first days of life due to potential risks of intracranial hemorrhage.[3]
Infusion-related cautions	May cause arrhythmias, apnea, or death if administered by rapid IV push.[4]
Dosage	**Prolong functional duration of arterial catheters:** 30 mg papaverine per 250 mL of heparinized (1 unit/mL) arterial catheter solution (e.g., NS or ½NS).[5,6] **Prevention of arterial spasm:** 1.5 mg/kg papaverine in 4 mL NS infused over 2 minutes (see Comments section)[7] given up to 4 times daily.[4]
Dosage adjustment in organ dysfunction	Discontinue use in patients with liver dysfunction or symptoms of hepatic hypersensitivity (i.e., GI symptoms, jaundice, or eosinophilia).[2]
Maximum dosage	6 mg/kg/day in children.[4] 120 mg/dose in *adults*.[2,4]
Additives	Contains edetate disodium. Multidose vials also contain chlorobutanol.[2]
Suitable diluents	NS, ½NS, D5W, D10W, D-R, D-S, R.[8]
Maximum concentration	30 mg/mL (undiluted) for vasospasm in *adults*.[2]
Preparation and delivery	**Stability:** Possible yellow discoloration does not appear to reflect a reduction in potency.[8] **Compatibility:** Incompatible in LR.[2]
IV push	Slowly over at least 1–2 minutes.[2]
Intermittent infusion	Dilute in 4 mL NS and infuse over at least 2 minutes.[7]
Continuous infusion	May be given continuously.[5,6]

Other routes of administration	IM.[2]
Comments	A study of single intra-arterial dose of papaverine given after cardiac catheterization did not demonstrate a reduction in pulse loss compared with heparin flush.[7]

Pegfilgrastim

Brand names	Neulasta, Pegylated GCSF, G-CSF (PEG Conjugate)
Medication error potential	Look-alike, sound-alike drug names. ISMP and USP report that Neulasta has been confused with Lunesta and Neumega. USP reports that Neulasta has been confused with Neupogen; no patient harm resulted.[1,2]
Contraindications and warnings	**Contraindications:** Individuals with known hypersensitivity to pegfilgrastim, filgrastim, or any component.[3] Do not use within 14 days before or 24 hours after administration of cytotoxic chemotherapy.[4] **Other warnings:** Rare cases of splenic rupture have been reported; some were fatal. Abdominal pain or shoulder pain that occurs after receiving pegfilgrastim should be evaluated.[3] Evaluate patients who develop fever and lung infiltrates or respiratory distress after dosing; acute respiratory distress syndrome (ARDS) has been reported. Discontinue pegfilgrastim if ARDS occurs.[3] Severe and fatal sickle cell crises may occur in patients with sickle cell disorders receiving filgrastim, the parent compound of pegfilgrastim.[3] Safety and efficacy have not been evaluated for use in peripheral blood progenitor cell mobilization or in patients receiving radiation therapy.[4]
Infusion-related cautions	Allergic reactions, including anaphylaxis may occur, especially with the initial dose. Epinephrine, antihistamines, corticosteroids, and/or bronchodilators are usually effective in alleviating symptoms.[4] Patients who have had severe reactions should not receive pegfilgrastim.[3,4]
Dosage	Consult individual protocol for complete dosing information. Do not administer within 14 days before or 24 hours after administration of cytotoxic chemotherapy.[3,4] Efficacy has been shown with q 2 wk chemotherapy regimens, but not with regimens under a 2-week duration.[5] **Children <45 kg:** 100 mcg/kg SC (maximum dose 6 mg) once per chemotherapy cycle, beginning 24–72 hours after completion of chemotherapy.[6–11] **Adolescents >45 kg and *adults*:** 6 mg SC once per chemotherapy cycle, beginning 24–72 hours after completion of chemotherapy.[3] **Mobilization for autologous stem cell transplant:** 100–300 mcg/kg SC (max dose 6 mg) once on day +3 after the end of chemotherapy.[12–14] A single dose of 300 mcg/kg SC with AMD3100 was used successfully in a 12-year old male with Ewing sarcoma who had failed mobilization with granulocyte colony-stimulating factor previously.[15] **Severe congenital neutropenia:** 100 mcg/kg SC q 9–12 days.[16]
Dosage adjustment in organ dysfunction	No dosage adjustment required.[3]
Maximum dosage	Not established. SC doses of up to 300 mcg/kg have been administered to *adult* patients without serious adverse effects.[3] Doses >6 mg are not recommended in children.[3] A 2-year old with congenital neutropenia accidentally received 937 mcg/kg (6 mg) with no adverse effects.[17]
Additives	Each prefilled syringe contains 0.35 mg acetate, 0.02 mg polysorbate 20, 0.02 mg sodium, and 30 mg sorbitol.[3]

Pegfilgrastim

Suitable diluents	None recommended.
Maximum concentration	0.1 mg/mL.[3]
Preparation and delivery	Administer undiluted. Do not shake syringe.[3]
IV push	Not recommended.
Intermittent infusion	Not recommended.
Continuous infusion	Not recommended.
Other routes of administration	SC as bolus injection.[3]
Comments	**Monitoring:** CBC count with differential and platelet count, temperature.[3] **Other:** The needle cover on the single-use prefilled syringe contains natural latex; persons with latex allergies should not receive the product.[3]

Peginterferon Alfa (Alpha-2a, Alpha-2b)

Brand names	PEGASYS (alpha-2a), PEG-Intron (alpha-2b)
Medication error potential	None noted.
Contraindications and warnings	**U.S. boxed warning:** Alpha interferons cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely, and periodic clinical and laboratory valuations should be performed. Treatment should be stopped in patients with persistently severe or worsening signs or symptoms of these conditions. In many cases, but not all, these disorders resolve after therapy is discontinued.[1,2] **Use with ribavirin[1,2]:** Ribavirin is mutagenic and genotoxic and is potentially carcinogenic. It may cause birth defects and/or fetal death; therefore, pregnancy should be avoided during ribavirin therapy. Ribavirin causes hemolytic anemia. **Contraindications:** Individuals with hypersensitivity to peginterferon alfa or any product components, autoimmune hepatitis, and decompensated liver disease.[1,2] Use of peginterferon alfa-2a (PEGASYS) in neonates and infants is contraindicated as this preparation contains benzyl alcohol.[2]
Infusion-related cautions	Not intended for IV use.
Dosage	**Interferon-pegylated alpha-2a (PEGASYS):** Body surface area (BSA) (m^2)/(1.73 m^2) × 180 mcg SC once a week for 48 weeks has been used as monotherapy in 14 children from 2–8 years old with chronic hepatitis C.[3] In children who have hepatitis C and who survived cancer, 0.5 mcg/kg (with daily ribavirin) has been used.[4] In older children and *adults* with thalassemia major and chronic hepatitis C, 180 mcg SC once a week for 24 weeks was used with placebo (n = 12) or ribavirin (n = 8).[5] While poor patient recruitment ended the study early, investigators concluded that the combination was probably safe and effective and could be considered in patients with thalassemia and moderate transfusional iron overload. **Duration of therapy depends on genotype[2]:** **Genotypes 1,4,5,6:** 48 weeks. **Genotypes 2,3:** 24 weeks. **Interferon-pegylated alpha-2b (PEG-Intron):** 1–1.5 mcg/kg SC once a week (with daily ribavirin) has been used in children 2–17 years of age with chronic hepatitis C.[6–9] In *adults*, monotherapy dosing is different from combination (with daily ribavirin) therapy dosing. Both monotherapy and combination therapy are based on weight and concentration of product.[2]
Dosage adjustment in organ dysfunction	**Peginterferon alpha-2a (PEGASYS)[1]** **Hematologic[1]** **Absolute neutrophil count (ANC)** **750–999/mm^3:** Weeks 1–2, decrease dose to 135 mcg/1.73 m^2 × BSA once weekly; weeks 3–48, no modification. **500–749/mm^3:** Weeks 1–2, hold until ANC >750/mm^3 then resume dose with 135 mcg/1.73 m^2 × BSA once weekly. Assess WBC count weekly for 3 weeks to verify ANC >750/mm^3. Weeks 3–48, 135 mcg/1.73 m^2 × BSA once weekly. **<250/mm^3 (or febrile neutropenia):** Discontinue treatment.

Peginterferon Alfa (Alpha-2a, Alpha-2b)

Dosage adjustment in organ dysfunction *(cont.)*

Platelets

≥50,000/mm³: Continue treatment.

<50,000/mm³: Decrease dose to 90 mcg/kg (50% decrease).

<25,000/mm³: Withhold treatment.

Renal: Use with caution and observe for toxicity in those with CrCl <50 mL/min. In *adults* with end-stage renal disease and on hemodialysis, the dose should be decreased to 135 mcg (a 25% decrease in usual dose of 180 mcg).

Hepatic: For increases in alanine aminotransferase (ALT), the dose should be decreased. If the increases in ALT are accompanied by increases in bilirubin or are progressive despite a decreased dose, the drug should be discontinued.

Peginterferon alpha-2b (PEG-Intron)[2]

Hematologic

Hemoglobin	<8.5 g/dL	Permanently discontinue
WBC	$<1.5 \times 10^9$/L	Reduce dose by 50%
	$<1.0 \times 10^9$/L	Permanently discontinue
Neutrophils	$<0.75 \times 10^9$/L	Reduce dose by 50%
	$<0.5 \times 10^9$/L	Permanently discontinue
Platelets	$<80 \times 10^9$/L	Reduce dose by 50%
	$<50 \times 10^9$/L	Permanently discontinue

Renal

CrCl 30–50 mL/min: Reduce dose by 25%.

CrCl 10–29 mL/min (including during hemodialysis): Reduce dose by 50%.

CrCl decreases during treatment: Discontinue.

Maximum dosage

Peginterferon (PEGASYS): 180 mcg daily for 1 week was given; no serious adverse effects were noted.[1]

Peginterferon alpha-2b (PEG-Intron): 3.45 mcg/kg/week over a period of 12 weeks; this overdosage did not result in serious adverse effects.[2]

Additives

Peginterferon alpha-2a (PEGASYS): Vials and prefilled syringes contain polysorbate 80 and benzyl alcohol.[1] (See Appendix C for specific information about potential benzyl alcohol toxicity in neonates.)

Peginterferon alpha-2b (PEG-Intron): Vials and syringes contain polysorbate 80.[2]

Suitable diluents

Not indicated.

Maximum concentration

Interferon-pegylated alpha-2a (PEGASYS): 180 mcg/mL.[1]

Interferon-pegylated alpha-2b (PEG-Intron): 150 mcg/0.5 mL (also available as 50, 80, and 100 mcg/0.5 mL).[2]

Peginterferon Alfa (Alpha-2a, Alpha-2b)

Preparation and delivery	**Peginterferon alpha-2a:** Single-use syringes or single-dose vials.[1] **Peginterferon alpha-2b (PEG-Intron REDIPEN and vials):** Single-use products, which do not contain preservatives. Once reconstituted, they should be used immediately or refrigerated and used within 24 hours.[2]
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	Not indicated.
Other routes of administration	Given by SC injection. IM not indicated.
Comments	Children may exhibit significant changes in body weight, linear growth, BMI, and body composition.[27] **Monitoring:** Routine monitoring should include CBC, chemistries (including liver function tests), thyroid-stimulating hormone, and triglycerides. **Drug interactions:** Interferon-pegylated alpha-2a (PEGASYS) increases theophylline area under the concentration curve by 25%. Theophylline serum concentrations should be monitored during treatment.[1]

Penicillin G Potassium/Sodium

Brand names

Pfizerpen; various generics

Medication error potential

USP reports confusion with ampicillin, oxacillin, and penicillamine.[1]

Contraindications and warnings

Contraindications: A history of a hypersensitivity (anaphylactic) reaction to any penicillin.[2,3]

Warnings: Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[3] These are more likely in patients who are sensitive to multiple allergens (e.g., asthma) and in those with a history of type I reaction to penicillin or cephalosporins.[2,3] (See Appendix C for specific information.)

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2,3] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2,3]

Infusion-related cautions

If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management. Large-dose penicillin therapy (i.e., >10 million units) should be administered slowly due to potential adverse effects of electrolyte imbalance from the potassium content.[4] The total dose of potassium or sodium content should influence the rate of administration.[4] (See Additives section.)

Dosage

Neonates

Congenital syphilis: If ≤7 days of age, give 100,000 units/kg/day divided q 12 hr for 10 days.[5] If >7 days of age, give 100,000–150,000 units/kg/day divided q 8 hr for 10 days.[5] If more than 1 day of therapy is missed, the entire therapy should be repeated.[5]

PNA	<1200 g	≤2000 g	>2000 g
≤7 days	50,000–100,000 units/kg/day divided q 12 hr[6,7]	50,000–100,000 units/kg/day divided q 12 hr[6,7]	75,000–150,000 units/kg/day divided q 8 hr[7]
>7 days	50,000–100,000 units/kg/day divided q 12 hr[6,7]*	75,000–150,000 units/kg/day divided q 8 hr[7]	100,000–200,000 units/kg/day divided q 6 hr[7]

*Until 4 weeks of age.

Meningitis: If ≤7 days of age and >2000 g, give 150,000 units/kg/day divided q 8–12 hr.[8] Smaller doses and prolonged intervals may be needed in very low birth weight infants. If ≥7 days of age, give 200,000 units/kg/day divided q 6–8 hr.[8] For documented Group B *Streptococcus*, give 250,000–450,000 units/kg/day divided q 8 hr (if ≤7 days of age) and 450,000–500,000 units/kg/day divided q 6 hr (if >7 days of age).[7]

Infants and children: Give 25,000–50,000 units/kg/day divided q 6 hr for mild-to-moderate infections[7] and 250,000–400,000 units/kg/day divided q 4–6 hr for severe infections.[7]

Bacterial endocarditis

Enterococcal endocarditis: 300,000 units/kg/day divided q 4–6 hr for 4–6 weeks (plus gentamicin 3 mg/kg/day divided q 8 hr for 2 weeks).[9]

Viridans group, streptococcal, or *S. bovis* (penicillin sensitive): 200,000 units/kg/day divided q 4–6 hr for 4 weeks if native valve and 300,000 units/kg/day divided q 4–6 hr for 6 weeks if prosthetic valve (with or without gentamicin 3 mg/kg/day divided q 8 hr for 2 weeks).[9]

Penicillin G Potassium/Sodium

Dosage *(cont.)*	**Viridans group, streptococcal, or *S. bovis* (relatively resistant):** 300,000 units/kg/day divided q 4–6 hr for 4 weeks for native valve and 6 weeks for prosthetic valve (plus gentamicin 3 mg/kg/day divided q 8 hr for 2 weeks).[9] **Congenital syphilis:** (>1 month after neonatal period) 200,000–300,000 units/kg/day divided q 4–6 hr for 10 days.[7] **Syphilis and early latent syphilis in children:** 50,000 units/kg IM, up to 2.4 milliunits in a single dose.[5] **Late latent syphilis or latent syphilis of unknown duration in children:** 50,000 units/kg IM up to 2.4 milliunits × 3 doses at weekly intervals.[5] **Meningitis:** Initial empiric therapy should be vancomycin plus a third-generation cephalosporin. If sensitive to penicillin, begin 250,000–400,000 units/kg/day (maximum 12–24 million units/day)[7,8] divided q 4–6 hr.[7,8]
Dosage adjustment in organ dysfunction	If CrCl is 10–50 mL/min, administer 75% of normal dose; if CrCl is <10 mL/min, give 20% to 50% of normal dose is recommended in *adults*.[10]
Maximum dosage	Not to exceed 24 million units/day.[7]
Additives	Each million units of penicillin G potassium contain 1.7 mEq potassium and 0.3 mEq sodium, and each million units of penicillin G sodium contain 1.68 mEq sodium.[2–4]
Suitable diluents	**Penicillin G potassium:** D2.5W, D5W, D10W, NS, LR, ½NS, D5NS, D5LR.[4] **Penicillin G sodium:** Variable stability in D5W, NS,[4] SW.[3] (See additional resource for more specific information.)
Maximum concentration	1 million units/mL.[2,3] 167,000 units/mL in SW results in a maximum recommended osmolality for peripheral infusion in fluid-restricted patients.[11]
Preparation and delivery	**Delivery system issues:** The mixing of penicillin with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside. (See Appendix C for more specific information.) **Stability:** Because of degradation or transformation penicillin G products form rapidly and may be responsible for sensitization, reconstituted solutions should be used immediately.[4] **Compatibility:** See Appendix D for PN compatibility information.[12]
IV push	Not recommended. Rapid administration of large doses my cause electrolyte imbalances due to the potassium content.[3] Cardiac arrest occurred in an infant who erroneously received 500,000 units/kg (containing 1 mEq/kg of potassium) over 2 minutes.[3]
Intermittent infusion	Infuse over 15–30 minutes.[4] The electrolyte (potassium or sodium) content should be considered when determining the infusion rate. (See Additives section.)
Continuous infusion	Not generally administered by this method; however, large doses may be given by continuous infusion.[2,4] Sensitization, due to degradation or transformation of penicillin G products, may be increased with continuous infusions over 6–24 hours.[13]

Penicillin G Potassium/Sodium

Other routes of administration	≤100,000 units/mL cause little discomfort when given IM.[2,4]

Comments

Rare adverse effects: Neurotoxic effects (e.g., lethargy, confusion, twitching, multifocal myoclonus, localized or generalized epileptiform seizures) may occur with large doses, especially in patients with renal insufficiency.[2,3,14–17]

Laboratory interference: False–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix, TEST-TAPE, Clinistix) based on enzymatic glucose oxidase reactions be used. Positive direct Coombs tests have been reported during treatment with penicillin.[2,3]

Other: Penicillin has been the drug of choice for *naturally* occurring anthrax; however, because of possible penicillin resistance or induction of resistance, the CDC does *not* recommend penicillin monotherapy to treat inhalational anthrax that occurs as the result of biologic warfare or bioterrorism.[18,19] Appropriate combination regimens include ciprofloxacin or doxycycline *and* one or two anti-infective agents that are predicted to be effective.

Pentamidine Isethionate

Brand names	Pentam 300
Medication error potential	None noted.
Contraindications and warnings	**Contraindications:** Patients with hypersensitivity to pentamidine isethionate.[1] **Warnings:** Fatalities due to hypotension, cardiac dysrhythmias, hypoglycemia, and acute pancreatitis have been reported.[1–6]
Infusion-related cautions	Severe hypotension, hypoglycemia, and cardiac arrhythmias have occurred following rapid administration.[1,3,4,7] Because of the risk of hypotension, the patient should be supine and have blood pressure monitored during IV infusion or IM injection.[1] After the dose is given, blood pressure should be monitored until stable.[1] Emergency equipment for resuscitation should be readily available. In some cases extravasation has resulted in severe tissue damage requiring surgical debridement and grafting.[1,8] There is no known antidote for treatment of extravasation and management should be symptomatic.
Dosage	***Pneumocystis jiroveci* pneumonia (PCP)** **Treatment (those who are intolerant of trimethoprim/sulfamethoxazole (TMP/SMX) or who do not respond to TMP/SMX):** 4 mg/kg IV daily for 14–21 days.[1,2,9] If there is clinical improvement after 7–10 days, oral atovaquone or trimethoprim/dapsone can be used to complete the treatment.[9] **Prophylaxis:** While IV pentamidine has been used, it is no longer recommended for PCP prophylaxis.[9] If TMP/SMX is not tolerated, aerosolized pentamidine 300 mg/dose monthly via the Respirgard II nebulizer can be used in children (usually >5 years of age) who are able to use the device.[2,9] One study evaluated 4 mg/kg IV given monthly in pediatric oncology patients intolerant of TMP/SMX.[10] Breakthrough PCP was higher in infants than in older children leading investigators to suggest that other options need to be investigated in infants.[10] **Leishmaniasis** **Cutaneous:** 2–3 mg/kg IV daily or every other day for up to 7 doses.[11,12] **Visceral:** Pentamidine 2 mg/kg IM every other day with daily allopurinol for 30 days was more effective than pentamidine 4 mg/kg every other day for 15 doses in antimony resistant disease in those 5–60 years old.[8]
Dosage adjustment in organ dysfunction	**CrCl 10–30 mL/min:** Usual dose q 36 hr.[13] **CrCl <10 mL/min:** Usual normal dose q 48 hr.[13] Neither the safety nor efficacy of dosage adjustments in renal or hepatic dysfunction is known.[1]
Maximum dosage	4 mg/kg.[1]
Additives	None.
Suitable diluents	D5W. Do not use NS to reconstitute because precipitation will occur.[1,14]

Pentamidine Isethionate

Maximum concentration	100 mg/mL for IM use. ~6 mg/mL for IV infusion.[1,11]
Preparation and delivery	**Preparation:** 3–5 mL SW is used to reconstitute the lyophilized powder (300 mg). Further dilution is required for IV infusion.[1,14] **Photosensitivity:** Protect from light during storage.[1]
IV push	Not indicated. Severe hypotension occurs with rapid infusion.[1]
Intermittent infusion	Over 60–120 minutes.[1]
Continuous infusion	Not indicated.
Other routes of administration	Deep IM in *adults*. To minimize local adverse effects, the Z-track injection technique should be used.[1] Nebulization.
Comments	Each 1.74 mg pentamidine isethionate is equivalent to 1 mg pentamidine.[1] **Adverse effects:** Renal toxicity is common following the use of parenteral pentamidine and usually occurs after 2 weeks of therapy.[1,9] Maintaining adequate hydration and monitoring electrolytes and renal function can help minimize these effects. Nephrotoxicity is usually reversible with discontinuation of the drug.[1] Hypoglycemia and hyperglycemia can occur with parenteral or inhalational therapy and may persist for months after discontinuation. Monitor serum glucose concentrations before, during, and after treatment with pentamidine. Use with caution in patients predisposed to hypoglycemia or hyperglycemia.[1] Perioral and facial paresthesias have been reported with the use of prophylactic IV pentamidine in pediatric patients. Symptoms resolved within 30 minutes after the infusion was discontinued.[15] **Monitoring:** Daily BUN, SCr, and blood glucose. Periodic assessment of CBC, liver function tests, serum calcium, and ECGs is also recommended.[1] **Drug interactions:** Nephrotoxic effects may be additive with use of other drugs with known nephrotoxicity such as amphotericin and the aminoglycosides.[1] Close monitoring of renal function is recommended should it be necessary to combine these agents.

PENTobarbital Sodium

Brand names	Nembutal Sodium
Medication error potential	Look-alike, sound-alike drug names. Tall man letters (not FDA approved) are recommended to decrease confusion between PENTobarbital and PHENobarbital.[1,2]
Contraindications and warnings	**Contraindications:** In patients with known hypersensitivity to barbiturates and in patients with a history of manifest or latent porphyria.[2] **Warnings:** May be habit forming. Should be withdrawn gradually if large doses have been used for prolonged periods.[2] Rapid administration may cause respiratory depression, apnea, laryngospasm, or vasodilation with hypotension.[2] Paradoxical excitement may occur or important symptoms could be masked when given to patients with acute or chronic pain.[2]
Infusion-related cautions	Respiratory depression and arrest requiring mechanical ventilation may occur. Monitor oxygen saturation. If hypotension occurs, the infusion rate should be decreased and/or the patient should be treated with IV fluids and/or vasopressors. PENTobarbital is an alkaline solution (pH = 9–10.5); therefore, extravasation may cause tissue necrosis.[2] Gangrene may occur following inadvertent intra-arterial injection.[2]
Dosage	**Procedural sedation:** 1–6 mg/kg over 30 seconds (≤50 mg/min).[3–11] If no response within 1 minute, give 1–2 mg/kg to desired effect.[12] Repeat up to a total dose of 7.5 mg/kg.[6] Patients chronically receiving barbiturates may require doses of 9 mg/kg.[6,9] **Sedation with mechanical ventilation:** A loading dose of 1–2 mg/kg followed by a continuous infusion of 1–2 mg/kg/hr.[9,11] Reload and titrate infusion to desired effect. **Medically-induced coma (for persistently elevated intracranial pressure (ICP) or refractory status epilepticus):** A loading dose of 15–35 mg/kg over 60–120 minutes[13–19] followed by 1.5–3.5 mg/kg/hr.[13–19] Reload and titrate infusion to desired effect. If hypotension occurs, decrease infusion rate or treat with IV fluids and vasopressors.
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal failure.[2,20] Use cautiously and decrease initial dose in hepatic dysfunction.[2]
Maximum dosage	**Sedation:** Total cumulative doses have ranged from 1.3–9.5 mg/kg,[3,8] with a mean of 4.4 mg/kg,[7] up to 100 mg/dose.[2,12] **Medically-induced coma:** Individualize therapy by titrating dosage based on EEG, ICP, cerebral perfusion pressure, and blood pressure.[16,21] Serum PENTobarbital concentrations of 20–40 mg/L should produce an isoelectric EEG.[18]
Additives	Contains propylene glycol (40% v/v).[2] (See Appendix C for specific information about propylene glycol potential for toxicity.)
Suitable diluents	D2.5W, D5W, D10W, LR, ¼NS, ½NS, NS, D5LR, D5¼NS, D5½NS, dextran 6%-D5, dextran 6%-D5NS, and dextran 6%-RL.[2,22,23]
Maximum concentration	50 mg/mL for intermittent infusion.[23]

PENTobarbital Sodium

Preparation and delivery	**Stability:** Store at room temperature (30°C). Brief exposure up to (40°C) does not adversely affect the product, but protect from freezing.[2] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Not recommended. Rapid infusion may cause hypotension and decreased myocardial contractility.[2,22]
Intermittent infusion	50 mg/mL given over 10–30 minutes[2] not to exceed 50 mg/min.[2] In order to decrease hypotension, a loading dose should be given over 60–120 minutes.[2,18]
Continuous infusion	50 mg/mL.[23]
Other routes of administration	2–6 mg/kg (not to exceed 100 mg) as a single injection given deep into a large muscle.[2] The volume of the injection at any one site should not exceed 5 mL.[2]
Comments	**Rare adverse effects:** Administration of large doses of PENTobarbital for more than 4 days may be associated with pulmonary edema, pneumonia, and ileus.[19] For these reasons, some practitioners suggest that tapering of PENTobarbital should be attempted 12 hours after a burst-suppression pattern is obtained on EEG.[14] Anticonvulsant hypersensitivity syndrome is an acute, life-threatening, idiosyncratic reaction that has been reported in patients receiving phenytoin, PHENobarbital, carbamazepine, primidone, and lamotrigine.[24–26] Symptoms generally develop within 1–12 weeks following initiation and include a classic triad of fever, rash, and lymphadenopathy.[24–26] Peripheral blood leucocytosis and eosinophilia and internal organ involvement may also be noted. Immediate discontinuation of the suspected anticonvulsant is essential for good outcome.[24–26] Cross-reactivity among the aromatic anticonvulsants has been noted; hence, these should not be used as alternative agents.[24–26] **Monitoring:** Large variability exists in patient response to initial and maintenance doses; hence, individualize dosage based on serum concentration, clinical response, and EEG pattern. Therapeutic serum concentrations are 1–5 mg/L (hypnotic) and 10–50 mg/L (coma).[22] **Drug interactions:** PENTobarbital is associated with numerous drug interactions[22]; consult appropriate resources for dosing recommendations before combining any drug with PENTobarbital. **Pharmacodynamics:** Neonates may have an increased risk for complications from PENTobarbital coma.[27] **Other:** One case report described PENTobarbital desensitization in a 3-month-old with refractory status epilepticus who had a known allergy to PHENobarbital.[28]

PHENobarbital Sodium

Brand names	Luminal Sodium
Medication error potential	Use tall man letters to decrease confusion between PENTobarbital and PHENobarbital.[1] Look-alike, sound-alike drug names. Confusion with pentobarbital, Phenergan, and phenytoin sodium has been noted. Confusion with phenytoin has resulted in patient harm and death.[2]
Contraindications and warnings	**Contraindications:** In patients with known hypersensitivity to barbiturates or any component of the formulation.[3] Should not be used in patients with a history of manifest or latent porphyria, marked hepatic impairment, dyspnea or airway obstruction, nephritic patients (large doses) or in those with a history of sedative/hypnotic addiction.[3] Should not be given intra-arterially or subcutaneously.[3] **Warnings:** May be habit forming.[3] Should be withdrawn gradually if large doses have been used for prolonged periods.[3] Rapid administration may cause respiratory depression, apnea, laryngospasm, or hypotension.[3] Paradoxical excitement may occur or important symptoms could be masked when given to patients with acute or chronic pain.[4] (See Rare Adverse Effects in the Comments section for information on suicide.)
Infusion-related cautions	May cause respiratory depression or apnea if administered too rapidly or when combined with other sedatives.[3] Extravasation may cause tissue necrosis.[4] Inadvertent intra-arterial injection can cause spasms, severe pain, and other symptoms (e.g., discolored skin or white hand with cyanosed skin) along the involved artery, which can result in local reactions varying from transient pain to gangrene.[3,4]
Dosage	**Hyperbilirubinemia:** Studies evaluating the use to prevent or treat neonatal hyperbilirubinemia and decrease the need for phototherapy and exchange transfusion are mixed.[5–8] 5 mg/kg/day within 6 hours of life for 5 days reduced the duration of phototherapy[6]; however, 5 mg/kg/day for 3 days did not decrease the need for phototherapy or exchange transfusion.[7] 12 mg/kg as a single dose within hours of life significantly increased the rate of bilirubin disappearance, but the effect was not noted until day 7.[8] A dose of 20 mg/kg followed by 5 mg/kg/day for 1 week did not produce a clinically important difference when used with phototherapy.[5] **Neonatal abstinence syndrome:** An opiate is the preferred initial therapy; however, addition of PHENobarbital may decrease severity.[9,10] A loading dose of 20 mg/kg followed by 2–6 mg/kg/day, with the first dose given 12–24 hours after the loading dose.[11] If the severity score is <8, then a serum concentration of 20 mg/L is adequate and the dose should be maintained for 72 hours.[11] If the score is >8, give 10 mg/kg q 12 hr until the syndrome is better or serum concentrations reach 70 mg/L.[11] Once the infant is stable for 72 hours, the dose should be decreased 15% per day.[11] When the severity score is <8 and serum concentration <15 mg/L, PHENobarbital should be stopped.[11] **Prophylactic seizure therapy in severe perinatal asphyxia:** There is little evidence from randomized controlled trials to support the use of any of the anticonvulsants.[12] 40 mg/kg/dose over 60 minutes given as soon as possible is associated with a 27% reduction in seizures and significant improvement in neurological outcome at 3 years of age.[13] Term infants with asphyxia had higher trough serum concentration than those without asphyxia[14] and require about half the maintenance dose of nonasphyxiated neonates.[15] **Seizures—nonstatus epilepticus** **Neonates:** Loading dose (see Seizures—status epilepticus below). Maintenance doses of 3.5–4.5 mg/kg/day if ≤35 weeks and 4–5 mg/kg/day if >35 weeks gestational age.[15] Dose >5 mg/kg/day are generally associated with toxicity.[16] Serum PHENobarbital concentrations should be >40 mg/L before an additional anticonvulsant is used.[17] **Infants and children:** Loading dose (see Seizures—status epilepticus below). Maintenance doses of ≤5 mg/kg/day.[18–20] If 1–5 years of age then 6–8 mg/kg/day, if 5–12 years of age then 4–6 mg/kg/day, and if 12 years of age give 1–3 mg/kg/day.[19] All doses may be given BID or once daily.[18–20]

Dosage *(cont.)*	**Seizures—status epilepticus (persistent or recurrent)** **Neonates:** Some suggest that a benzodiazepine is the initial treatment of choice.[21] A loading dose of 8–10 mg/kg/day for 2 days,[22] 15–20 mg/kg,[16,23] or 30 mg/kg[24] has been suggested. Maintenance dose of ≤5 mg/kg/day divided BID or given once daily.[25] **Infants and children:** Some suggest that this should only be used when maximum doses of benzodiazepine and hydantoin have failed.[24] Loading dose of 20 mg/kg[25–27] up to 1000 mg.[26] Some advocate an additional 20 mg/kg/dose if no response within 15 minutes.[26] **Refractory status:** May use a continuous infusion of a short-acting barbiturate. (See Pentobarbital monograph). 10 mg/kg/dose q 30 min (maximum 120 mg/kg in 24 hours),[28] 5–10 mg/kg/dose to a total dose of 80 mg/kg.[30] (See Maximum Dosage section.) **Maintenance dose:** See Seizures—nonstatus epilepticus above.
Dosage adjustment in organ dysfunction	Adjust dosage using serum concentrations in patients with severe renal dysfunction.[29] If CrCl <10 mL/min, give 50% of normal dose q 24 hr.[29] Larger dosages are necessary in children undergoing continuous cycling peritoneal dialysis[30] and in neonates on extracorporeal membrane oxygenation.[31,32]
Maximum dosage	<30[24]–40[21,26] mg/kg as a loading dose. Up to 300 mg/dose[3] or 1 g/dose[22] for status epilepticus. Total doses of 70–120 mg/kg were given over 24 hours to children with refractory status epilepticus.[28,33] Because of interpatient variability in PHENobarbital elimination, individualize dosage based on serum concentrations.
Additives	May contain benzyl alcohol and/or propylene glycol.[3] (See Appendix C for specific information about benzyl alcohol propylene glycol potential for toxicity.)
Suitable diluents	May be diluted with an equal volume of D2.5W, D5W, D10W, RI, LR, NS, ½NS, D-R, D-LR, D-saline combinations, dextran 6%-D5W, and dextran 6%-LR.[34]
Maximum concentration	130 mg/mL.[34]
Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information. **Photosensitivity:** Protect from light.
IV push	Not recommended.
Intermittent infusion	<30, 60, 65, or 130 mg/mL undiluted (available commercially)[3] and infuse over 3–5 minutes, not to exceed 30 mg/min[5] or 50–75 mg/min[3,25] or 1 mg/kg/min[4] to 2 mg/kg/min.[24] Large loading doses (e.g., 40 mg/kg) may be infused over 60 minutes.[13]
Continuous infusion	No information available.
Other routes of administration	May be given IM deep into muscle at a volume <5 mL.[3]

PHENobarbital Sodium

Comments

Rare adverse effects

Anticonvulsant hypersensitivity syndrome: An acute, life-threatening, idiosyncratic reaction that has been reported in patients receiving phenytoin, PHENobarbital, carbamazepine, primidone, and lamotrigine.[35–37] Symptoms generally develop within 1–12 weeks following initiation and include a classic triad of fever, rash, and lymphadenopathy.[35–37] Peripheral blood leucocytosis and eosinophilia and internal organ involvement may also be noted. Immediate discontinuation of the suspected anticonvulsant is essential for good outcome.[35–37] Cross-reactivity among the aromatic anticonvulsants has been noted; hence, these should not be used as alternative agents.[35–37]

Suicidal behavior/ideation: The incidence of this adverse effect has been noted to be greater than placebo (0.43% versus 0.24% risk) in patients receiving 11 anticonvulsants (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy for the treatment of epilepsy, psychiatric disorders, and other conditions.[38] The FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality.

Monitoring: Large variability exists in patient response to initial and maintenance dosages; individualize dosage based on serum concentration and clinical response. Therapeutic serum concentration is 15–40 mg/L. Significantly higher serum concentrations are required if used for medically induced coma (>100 mg/L with no reflexes).

Drug interactions: PHENobarbital is a substrate for CYP2C9, CYP2C19, and CYP2E1.[4] Because PHENobarbital induces the CYP1A2; CYP2A6, CYP2C8, CYP2C9 and CYP3A4, and UGT, it is associated with numerous drug interactions[4]; consult appropriate resources for dosing recommendations before combining any drug with PHENobarbital.

Phenylephrine

Brand names	Generic
Medication error potential	One source reports confusion of phenylephrine with phentolamine, epinephrine, norepinephrine, and Phenergan.[1]
Contraindications and warnings	**Contraindications:** Should not be used in severely hypertensive patients, those with ventricular tachycardia, or those allergic to phenylephrine or any of its components.[2] **Warnings:** Contains sodium metabisulfate, which may cause allergic reactions in those susceptible. Anaphylaxis may occur.[2]
Infusion-related cautions	None reported.
Dosage	Limited information is available in pediatric patients. **Hypotension:** 0.1 mg/kg IM or SC. Additional IM or SC doses may be given in 1–2 hours if needed.[3] 0.1–5 mcg/kg/min IV continuous infusion titrated to target blood pressure.[4–8] **Hypotension during spinal anesthesia:** 0.044–0.088 mg/kg SC or IM.[2]
Dosage adjustment in organ dysfunction	None reported, titrate dose.
Maximum dosage	**Maximum initial dose IV:** 0.5 mg; maximum initial dose SC or IM is 5 mg.[2] Use of up to 15 mcg/kg/min by continuous infusion has been reported in a child.[9]
Additives	Each mL of phenylephrine contains 3.5 mg sodium chloride.[2] Contains sodium metabisulfite.[2,10]
Suitable diluents	D5W, NS.[2]
Maximum concentration	10 mg/mL.[2]
Preparation and delivery	**Photosensitivity:** Protect from light.[10]
IV push	May be administered by rapid IV injection in emergency situations. A maximum dose of 1 mg should not be exceeded by this route.[2]
Intermittent infusion	Dilute each mL (10 mg) phenylephrine with 9 mL SW for intermittent IV administration.[2,10]
Continuous infusion	May be given by continuous infusion diluted to 0.02 mg/mL.[2]

Other routes of administration	May be given SC or IM.[2]
Comments	**Monitoring:** Blood pressure should be monitored and phenylephrine titrated to effect. **Drug interactions:** Monoamine oxidase inhibitors markedly potentiate the effect of sympathomimetic pressor amines.[2]

Phenytoin Sodium

Brand names	Dilantin, Phenytek
Medication error potential	Look-alike, sound-alike drug names. Confusion has been noted between Feldene, fluconazole, fosphenytoin, nystatin, phenazopyridine, PHENobarbital, and phytonadione.[1] Dilantin has been mistaken for Diflucan, Dilaudid, Diltiazem, Neutrontin, and Nystatin.[1] Confusion with fosphenytoin and PHENobarbital has resulted in patient harm, and confusion with PHENobarbital has resulted in death.[1]
Contraindications and warnings	**Contraindications:** Phenytoin is contraindicated in patients with a history of hypersensitivity to hydantoin products.[2] Parenteral phenytoin effects ventricular automaticity and is contraindicated in patients with sinus bradycardia, sinoatrial block, second- and third-degree atrioventricular block, and Adams-Stokes syndrome.[2] **Warnings:** IV rate of administration should not exceed 50 mg/min in *adults* and 1–3 mg/kg/min in neonates.[2] Phenytoin should be used cautiously in patients with hypotension and severe myocardial insufficiency. The FDA is investigating the possibility of an increased risk of serious skin reactions (e.g., Stevens-Johnson syndrome and toxic epidermal necrolysis) in patients given phenytoin who have the human leukocyte antigen allele HLA-B*1502.[3] This allele occurs almost exclusively in individuals with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais.[3] Until the FDA evaluation is finalized, phenytoin should be avoided as an alternative for carbamazepine in patients who test positive for HLA-B*1502.[3] (See Monitoring in the Comments section.) A relationship between phenytoin and the development of localized or generalized lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin disease has been noted.[2] Lymph node involvement may occur with or without symptoms and signs resembling anticonvulsant hypersensitivity syndrome. (See Comments section.)
Infusion-related cautions	Rapid administration has resulted in hypotension, cardiovascular collapse, and CNS depression.[2] Purple glove syndrome is the development of progressive distal limb edema, discoloration, and pain after peripheral administration of IV phenytoin.[4,5] Although this may occur from a reaction of the interstitial tissue to extravasation of phenytoin, it can occur in the absence of infiltration. It may result in extensive skin necrosis, limb ischemia, and compartmental syndrome, which may necessitate fasciotomies, skin grafting, or limb amputation. (See Appendix E for management.) Because of the high risk of extravasation and local tissue irritation with peripheral administration of phenytoin, especially in neonates with peripheral scalp IV lines, fosphenytoin should be considered. (See Fosphenytoin monograph.)
Dosage	In obese patients with active seizures the loading doses should be calculated on adjusted body weight using the following equation[5] (see Appendix B): Dosing weight (kg) = Ideal Body Weight (IBW) + 1.33 (measured weight – IBW) **Arrhythmias (Class 1B) (digoxin-induced tachyarrhythmias):** 1.25 mg over 5 minutes. May repeat every 5 minutes titrated to a total of 15 mg/kg.[6] **Post-traumatic epilepsy (see status epilepticus for dosing):** Although prophylactic phenytoin has been used for the prevention of epilepsy following head trauma, its use is controversial.[7–9] There are no compelling data in the pediatric literature to show that such treatment reduces the long-term risk of post-traumatic epilepsy or improves long-term neurologic outcome. It should *not* be used for the prevention of late epilepsy.[10] Children with severe, acute neurotrauma have markedly altered protein binding and phenytoin metabolism and may require larger doses and more frequent dosing.[9,11] Free serum phenytoin concentration should be monitored.[10]

Dosage *(cont.)*	**Status epilepticus** **Loading dose (assumes no previous phenytoin)** **Neonates:** 8–20 mg/kg[2,12,13] (may prefer PHENobarbital or a benzodiazepine). **Infants and children:** 10–20 mg/kg[14–16] not to exceed 1 g.[16] **Adolescents and *adults*:** 10–15 mg/kg not to exceed 1 g.[2] **Maintenance dose** **Neonates:** 4–8 mg/kg/day divided q 12–24 hr.[13,17] Some suggest smaller doses of 3–5 mg/kg/day.[12] Extremely difficult to obtain serum concentrations following conversion to oral therapy; therefore, consider an alternative anticonvulsant for oral dosing.[10,12,18] **Infants and children:** For 4 weeks to <1 years, 4–8 mg/kg/day.[12] For 1–12 years, 8–10 mg/kg/day divided q 8 hr.[12,14,16] **Adolescents and *adults*:** If ≥12 years, 4–8 mg/kg/day divided q 8–12 hr.[12] The manufacturer recommends 100 mg q 6–8 hr.[2]
Dosage adjustment in organ dysfunction	Dosage adjustment may be required in patients with hepatic[2] or renal dysfunction.[19,20]
Maximum dosage	20 mg/kg as a single dose, not to exceed 1 g.[21,22] Doses as large as 25 mg/kg/day divided q 6 hr were used to achieve total serum phenytoin concentrations within the "therapeutic range" in a neonate.[22] If large doses are used, free phenytoin concentrations should be monitored. Because of age-dependent variation in phenytoin elimination, individualize dosage based on total or free serum concentrations.
Additives	Undiluted injection contains 0.2 mEq sodium/mL of phenytoin.[23] Contains 40% propylene glycol. (See Appendix C for specific information about propylene glycol and potential for toxicity.)
Suitable diluents	Phenytoin is highly unstable in any IV solution; therefore, use only NS for dilution and do not mix with other medications.[23] An in-line 0.22–5 micron filter is recommended due to the high potential for precipitation of the solution.[23]
Maximum concentration	50 mg/mL (commercially available).[2]
Preparation and delivery	**Stability:** Use only a clear solution that is free from haziness or precipitant.[23] Although a faint yellow color may develop, this has no effect on potency.[23] Upon refrigeration or freezing, a precipitate might form; however, this will dissolve when allowed to stand at room temperature.[23] No evidence of DEHP leaching from PVC bag.[23] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Not recommended.[2]
Intermittent infusion	≤50 mg/mL.[2] If necessary, dilute with NS[2,23] to a concentration <6 mg/mL and infuse at a rate of 1–3 mg/kg/min in neonates, infants, and young children[2] or 50 mg/min in older children and *adults*.[2] Following administration, flush needle or catheter with NS.

Phenytoin Sodium

Continuous infusion Not recommended.[2]

Other routes of administration The manufacturer suggests that IM administration is acceptable but does not recommend it for the treatment of status epilepticus.[2] Most practitioners would not administer phenytoin IM because of severe pain at the injection site, erratic absorption, possible precipitation of drug in tissue and severe damage due to infiltration.[24] Has been given IO.[25]

Comments

Rare adverse effects

Anticonvulsant hypersensitivity syndrome: An acute, life-threatening, idiosyncratic reaction that has been reported in patients receiving phenytoin, PHENobarbital, carbamazepine, primidone, and lamotrigine.[26–28] Symptoms generally develop within 1–12 weeks following initiation and include a classic triad of fever, rash, and lymphadenopathy.[26–28] Peripheral blood leucocytosis and eosinophilia and internal organ involvement may also occur. Immediate discontinuation of the suspected anticonvulsant is essential for good outcome.[28–30] Cross-reactivity among the aromatic anticonvulsants has been noted; hence, these should not be used as alternative agents.[26–28]

Abrupt discontinuation of phenytoinmay increase seizure frequency and/or precipitate status epilepticus. If an allergic or hypersensitivity reaction or if a life-threatening adverse event occurs, rapid substitution of an alternative anticonvulsant may be necessary. If phenytoin is discontinued due to development of a rash, an anticonvulsant *not* belonging to the hydantoin family and one structurally dissimilar should be used.[26–28]

Suicidal behavior/ideation: The risk of this adverse effect has been noted to be greater than placebo (0.43% versus 0.24% risk) in patients receiving 11 anticonvulsants (i.e., carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy for the treatment of epilepsy, psychiatric disorders, and other conditions.[3] The FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicide.

Monitoring: Because large variability exists in patient response to dose, individualize dosage based on serum concentration and clinical response. Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution and unbound phenytoin concentrations may be more useful.[18] Free phenytoin serum concentrations should be measured in newborns, in patients with renal dysfunction, or in those who are hypoalbuminemic because of decreases in protein binding, increases in volume of distribution, and altered clearance.[10,18] Continuously monitor of blood pressure, respiratory function, heart rate, and ECG during IV loading doses and for approximately 10–20 minutes after the end of an infusion.[2] If the heart rate decreases by more than 10 beats/min, the infusion rate should be decreased.[29]

The FDA does not recommend testing for the presence of *HLA-B*1502* prior to initiating phenytoin.[2]

Drug interactions: Because phenytoin induces the CYP2C19 and CYP3A families and UGT, it is associated with numerous drug interactions.[30] Phenytoin may also serve as a substrate and can be inhibited or induced by other drugs.[30] Consult appropriate resources for dosing recommendations before combining any drug with phenytoin.

Laboratory interference: Phenytoin may cause decreased serum levels of protein-bound iodine.[2] It may also produce lower than normal values for dexamethasone or metyrapone tests and may increase serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase.[2]

Physostigmine Salicylate

Brand names	Antilirium, generic
Medication error potential	Look-alike, sound-alike drug names. Physostigmine has been confused with pyridostigmine or Prostigmin; however, no patient harm resulted.[1]
Contraindications and warnings	Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be available as it is an antagonist and antidote for physostigmine. Contraindicated in asthma, gangrene, diabetes, cardiovascular disease, and mechanical obstruction of the GI or urogenital tract.[2] It should not be used in patients receiving choline esters or depolarizing neuromuscular blocking agents (e.g., decamethonium, succinylcholine).[2]
Infusion-related cautions	Bradycardia, asystole, convulsions, and hypersalivation have occurred following rapid injection.[2–4] Use appropriate precautions when handling and disposing of physostigmine as topical absorption can produce severe adverse effects (i.e., seizures, bradycardia).
Dosage	**Anticholinergic toxicity (reserve for life-threatening situations):** *Physostigmine overdose may precipitate a cholinergic crisis (salivation, emesis, urination and defecation).*[2] *Atropine sulfate injection should be available as an antagonist and antidote for life-threatening symptoms due to physostigmine.*[2,4] *The dose of atropine should be 50% of the administered dose of physostigmine.*[4] **Pediatric patients:** 0.02 mg/kg up to 0.5 mg/dose given over 3–5 minutes. If toxic effects persist, give 0.5 mg q 5–10 min up to 2 mg maximum dose.[3–9] **Adolescents and *adults*:** 1–2 mg. If toxic effects persist, give 1 mg q 10–20 min up to 4 mg.[3,4,6,7,10] Reduce dosage if nausea, vomiting and salivation occur.
Dosage adjustment in organ dysfunction	No information is available regarding dosage adjustment in organ dysfunction.
Maximum dosage	2 mg in pediatric patients[3,4,6,7,9] and 4 mg in adolescents or *adults*.[4] No maximum cumulative dose established. A total of 22 mg was administered IV over 48 hours to a 22-year-old patient.[11]
Additives	Contains 2% benzyl alcohol as a preservative and 0.1% sodium metabisulfite.[2] Physostigmine should not be withheld from an individual with life-threatening anticholinergic toxicity who is sulfite sensitive,[3] but epinephrine should be available. (See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates and sulfites.)
Suitable diluents	D5W, NS.[12]
Maximum concentration	1 mg/mL.[2]
Preparation and delivery	Have atropine on hand.[2] (See Infusion-Related Cautions section.)

Physostigmine Salicylate

IV push	Not recommended.[2] (See Infusion-Related Cautions section.)
Intermittent infusion	1 mg/mL or dilute with 10-mL suitable diluent and infuse over 5–10 minutes, not to exceed 0.5 mg/min in children or 1 mg/min in *adults*.[2]
Continuous infusion	0.02 mg/mL in D5W has been given by continuous infusion to a 20-year-old.[12]
Other routes of administration	May be given IM at same doses as IV.[2]

Comments

Significant adverse effects: Two *adults* developed sinus bradycardia after receiving physostigmine for tricyclic overdose. Following 1 mg of atropine, both patients developed asystole.[13]

Other: Although physostigmine has been used previously for tricyclic antidepressant toxicity in *adults* and children,[9,14] it now is recommended only for life-threatening symptoms unresponsive to other therapies.

The use of physostigmine in the central anticholinergic syndrome has been described in an infant and a child.[15,16]

Physostigmine successfully treated postanesthesia emergence delirium (cognitive and psychomotor deficits, irritability, anxiety, apathy, and sleep disturbances, including nightmares) in a randomized, controlled trial in children 1–5 years of age. The dose of physostigmine was 0.03 mg/kg in NS given over 1 minute. Nausea and vomiting was increased in children receiving physostigmine. The authors suggested increasing the infusion to 5 minutes and giving dexamethasone to prevent these symptoms.[17]

Piperacillin Sodium

Brand names	Pipracil
Medication error potential	Look-alike, sound-alike drug names. USP reports confusion with ampicillin and ticarcillin.[1]
Contraindications and warnings	**Contraindications:** In those with a history of allergic reactions to any of the beta-lactams, including penicillins and/or cephalosporins.[2] **Warnings** **Allergic reactions:** Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[2] These are more likely in patients who are sensitive to multiple allergens and in those with a history of penicillin, cephalosporins, or other beta-lactam hypersensitivity.[2] **Superinfection:** Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2] Antibiotic use that is not directed against *C. difficile* may need to be discontinued.[2]
Infusion-related cautions	Thrombophlebitis has been reported in 4% of patients.[2]
Dosage	**Neonates:** 200 mg/kg/day (400 mg/kg/day for meningitis) divided q 12 hr.[3] If <36 weeks gestational age (WGA), give 150 mg/kg/day divided q 12 hr for 1 week and then 225 mg/kg/day divided q 8 hr.[4] If >36 WGA, give 225 mg/kg/day divided q 8 hr for 1 week and then 300 mg/kg/day divided q 6 hr.[4] **Infants and children** **Mild-to-moderate infections:** 100–150 mg/kg/day divided q 6 hr, up to 8 g/day.[5] **Severe infections:** 200–300 mg/kg/day divided q 4–6 hr, up to 24 g/day.[5,6] **Appendectomy (perforated):** 200 mg/kg/day divided q 8 hr.[7] **Cystic fibrosis:** 350–500 mg/kg/day divided q 4–6 hr.[8,9] **Febrile neutropenia:** Administer 300 mg/kg/day divided q 8 hr in conjunction with other antibiotics.[10,11] **Perioperative prophylaxis:** 2 g 30 minutes before the procedure has been given to adolescents.[12]
Dosage adjustment in organ dysfunction	If CrCl is 30–50 mL/min, give normal dose q 8 hr; if CrCl is <30 mL/min, give q 12 hr.[13,14]
Maximum dosage	500 mg/kg/day.[8]
Additives	Contains 1.85 mEq sodium/g of piperacillin sodium.[2,15]
Suitable diluents	D5NS, D5W, NS, LR, BW, or Dextran 6% NS.[2,15]

Piperacillin Sodium

Maximum concentration	200 mg/mL for IV push,[2,15] 163 mg/mL for IV infusion,[15] and 400 mg/mL for IM administration.[2,15]
Preparation and delivery	**Delivery system issues:** The mixing of piperacillin with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[2,15] (See Appendix C for more specific information.) **Stability:** Use immediately after reconstitution.[2] Unused portion that has been stored at room temperature (20°C to 25°C) for 24 hours or after 48 hours if refrigerated (2°C to 8°C) should be discarded.[2] **Compatibility:** See Appendix D for PN compatibility information.[16]
IV push	200 mg/mL infused over 3–5 minutes.[2,15]
Intermittent infusion	10–20 mg/mL over 20–30 minutes.[2,15]
Continuous infusion	Piperacillin/tazobactam and other beta-lactam antibiotics have been given by this method.[17–20]
Other routes of administration	May be given by IM administration using 400 mg/mL in SW, NS, bacteriostatic SW or NS, D5W or D5NS, or lidocaine HCl 0.5% to 1% (without epinephrine).[2,15] Should be injected deep into the upper-outer quadrant of the buttock. Maximum dose injected into one site should not exceed 2 g.[2,15]
Comments	**Rare adverse effects:** Piperacillin is more allergenic (e.g., fever, rash) in patients with cystic fibrosis.[21] Serum-like sickness and coagulopathy associated with fever, rash, and abnormal liver function tests occurred in two patients with cystic fibrosis.[22] Patients with cystic fibrosis may be more susceptible to piperacillin–induced immune mediated hemolysis.[23] Abnormal coagulation tests (e.g., clotting time, platelet aggregation, and prothrombin time) may occur,[2] especially in patients with cystic fibrosis[22] or renal failure.[2] Piperacillin should be discontinued if bleeding occurs.[2] Tonic-clonic seizures have been reported in an 11-year-old child receiving IV piperacillin (3 g q 4 hr) over 30 minutes.[24] **Monitoring:** Coagulation parameters should be monitored frequently during simultaneous administration of large doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.[2] **Drug interactions:** Piperacillin may decrease the clearance of methotrexate.[2,25] Perioperative use of piperacillin may prolong the neuromuscular blockade of vecuronium or other nondepolarizing muscle relaxants.[2,26] Probenecid may decrease the clearance of piperacillin.[2] Consult appropriate resources for dosing recommendations before combining any drug with piperacillin. **Laboratory interference:** A false–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix or TEST-TAPE) based on enzymatic glucose oxidase reactions be used.[2] Piperacillin/tazobactam may cause a false–positive *Aspergillus* infection result when performed with the Bio-Rad Laboratories Platelia *Aspergillus* EIA test; hence, interpret reports cautiously and confirmed by other diagnostic measures.[2]

Piperacillin Sodium–Tazobactam Sodium

Brand names	Zosyn
Medication error potential	Look-alike, sound-alike drug names. USP reports confusion between piperacillin and nafcillin.[1] Zosyn has been confused with cefazolin, Unasyn, Zofran, and Zyvox.[1]
Contraindications and warnings	**Contraindications:** In those with a history of allergic reactions to any of the beta-lactams, including penicillins and/or cephalosporins.[2] **Warnings** **Allergic reactions:** Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[2] These are more likely in patients who are sensitive to multiple allergens (e.g., asthma) and in those with a history of penicillin, cephalosporins, or other beta-lactam hypersensitivity.[2] **Superinfection:** Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea, which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] Antibiotic use that is not for treatment of *C. difficile* may need to be discontinued.[2]
Infusion-related cautions	If given to a patient with known penicillin hypersensitivity, closely observed for allergenicity.[2] Anaphylactic reactions require immediate treatment with epinephrine. Oxygen, IV steroids, and airway management may be indicated.[2] Thrombophlebitis has been reported in 4% to 13% of patients.[2]
Dosage	Tazobactam is a beta-lactamase inhibitor that extends the spectrum of piperacillin but has little antibacterial activity. Piperacillin/tazobactam is available in a ratio of 8:1 (piperacillin:tazobactam).[2] *Doses are based on piperacillin component*.[2] **Neonates:** Safety in patients <2 months of age has not been established.[2] 100–300 mg/kg/day divided q 8–12 hr.[3–5] **Infants and children:** Inappropriate in mild-to-moderate infections.[6] For severe infections in those 2–9 months of age, give 240 mg/kg/day divided q 8 hr up to 18 g/day.[2,6] In those >9 months of age (up to 40 kg), give 300 mg/kg/day divided q 8 hr up to 18 g/day.[2,6] Those weighing more than 40 kg should receive *adult* dose of 12 g/day divided q 6 hr.[2] Based on a single-dose pharmacokinetic study, doses of 100 mg/kg q 8 hr for bacteria whose minimum inhibitory concentration (MIC) is 2 mg/L and q 6 hr if the MIC is between 4 and 8 mg/L should be effective.[7] **Cystic fibrosis:** 350–450 mg/kg/day divided q 6 hr.[8,9]
Dosage adjustment in organ dysfunction	If CrCl is 30–50 mL/min, give 140–200 mg/kg/day divided q 6 hr; if CrCl is 10–29 mL/min, give 140–200 mg/kg/day divided q 8 hr; and if CrCl is <10 mL/min, give 140–200 mg/kg/day divided q 12 hr.[10] No adjustment necessary in liver impairment.[2,11]
Maximum dosage	400 mg/kg/day[7,8] up to 16 g of piperacillin component daily.[11]
Additives	2.79 mEq of sodium/g of piperacillin.[2]
Suitable diluents	NS, SW, bacteriostatic water, bacteriostatic NS, and D5W.[12]

Piperacillin Sodium–Tazobactam Sodium

Maximum concentration	200 mg/mL (piperacillin component); however, further dilution in 50–150 mL is recommended.[2]
Preparation and delivery	**Delivery system issues:** The mixing of piperacillin with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside.[13–17] (See Appendix C for more specific information.) **Stability:** Thaw frozen container at room temperature (20°C to 25°C) or under refrigeration (2°C to 8°C).[12] Do not force thaw by immersion in water baths and do not microwave.[12] Do not refreeze.[12] **Compatibility:** See Appendix D for PN compatibility information.[18] Although amikacin and gentamicin are compatible in vitro for Y-site infusion, reformulated Zosyn contains EDTA, which is not compatible with tobramycin.[2]
IV push	Not administered by this method.
Intermittent infusion	Infuse over at least 30 minutes.[2,12]
Continuous infusion	Continuous infusions of 8–13.5 g piperacillin/24 hr have been studied in *adults*.[19–21] Prolonged infusions over 4 hours have also been studied in *adults*.[22] In a pediatric pharmacokinetic modeling study, continuous or prolonged infusions showed benefit over standard 30-minute infusion times.[23]
Other routes of administration	None.
Comments	**Rare adverse effects:** Piperacillin is more allergenic (e.g., fever, rash) in patients with cystic fibrosis.[24] Serum-like sickness and coagulopathy associated with fever, rash, and abnormal liver function tests occurred in two patients with cystic fibrosis.[25] Abnormal coagulation tests (e.g., clotting time, platelet aggregation, and prothrombin time) may occur, especially in patients with cystic fibrosis[2,25] or renal failure.[2] Piperacillin should be discontinued if bleeding occurs.[2] Tonic-clonic seizures have been reported in an 11-year-old child receiving IV piperacillin (3 g q 4 hr) over 30 minutes.[26] **Monitoring:** Coagulation parameters should be frequently monitored during coadministration with large doses of heparin, oral anticoagulants, or other drugs that may affect the blood coagulation system or the thrombocyte function.[2] **Drug interactions:** Piperacillin may decrease the clearance of methotrexate.[2,27] Perioperative use of piperacillin may prolong the neuromuscular blockade of vecuronium or other nondepolarizing muscle relaxants.[2,28] Probenecid may decrease the clearance of piperacillin.[2] Consult appropriate resources for dosing recommendations before combining any drug with piperacillin–tazobactam. **Laboratory interference:** A false–positive urinary glucose results when cupric sulfate solution-based tests (Clinitest, Benedict's solution, Fehling's solution) are used.[2] It is recommended that glucose tests (Diastix or TEST-TAPE) based on enzymatic glucose oxidase reactions be used.[2] Piperacillin–tazobactam may cause a false–positive *Aspergillus* infection result when performed with the Bio-Rad Laboratories Platelia Aspergillus EIA test; hence, interpret reports cautiously and confirmed by other diagnostic measures.[2]

Potassium Chloride

Brand names	Various manufacturers
Medication error potential	High-alert medication that has an increased risk of causing significant patient harm if used in error.[1] Look-alike, sound-alike drug names. Potassium chloride has been confused with metronidazole, potassium acetate, potassium bicarbonate, potassium citrate, potassium phosphates, and sodium chloride, and patient harm did not occur.[2]
Contraindications and warnings	**Contraindications:** Potassium chloride for injection is contraindicated in disease where high potassium levels may be encountered and in patients with hyperkalemia, renal failure, and in conditions in which potassium retention is present.[3] **Warnings:** Administration of potassium chloride at excessive rates may result in fatal dysrhythmias.[4] The rate of infusion should not exceed 0.5–1 mEq/kg/hr, and all sources should be considered.[5–8] ECG monitoring should accompany infusions ≥0.5 mEq/kg/hr. Some products contain aluminum.[3]
Infusion-related cautions	The injections are very hypertonic (i.e., the concentration of 2 mEq/mL has an osmolarity of 4000 mOsm/L) and must be diluted before administration.[3,9] Due to the increased occurrence of phlebitis with higher potassium concentrations, the product labeling recommends limiting concentrations to 40 mEq/L for peripheral administration when the serum potassium >2.5 mEq/L.[3] Extravasation may cause tissue sloughing and necrosis.[10] (See Appendix E for management of extravasation.)
Dosage	**Daily requirements (neonates, infants, children):** 2–5 mEq/kg/day.[11] **Hypokalemia:** 0.5–1 mEq/kg given over ≥2 hours.[5,7] During loop and thiazide diuretic therapy, larger doses may be required.[8]
Dosage adjustment in organ dysfunction	Potassium is renally eliminated; therefore, extreme caution is required when dosing patients with renal insufficiency.[3] In six 19- to 37-year-old *adults* with sickle cell disease and normal glomerular filtration, urinary potassium excretion was significantly less than individuals without sickle cell disease during an infusion of 0.75 mEq/kg over 2 hours.[12]
Maximum dosage	Close monitoring of ECG and serum concentrations is required. Dosage requirements are based on serum potassium concentrations. Intermittent infusions should not exceed 1 mEq/kg/hr including all sources. **Serum potassium >2.5 mEq/L:** 10 mEq/hr up to 200 mEq/day in *adults*.[3] **Serum potassium <2.0 mEq/L:** 40 mEq/hr up to 400 mEq/day.[3]
Additives	Multidose vials contain methylparaben 0.05% and propylparaben 0.005%.[3] (See Appendix C for specific information about potential paraben toxicity. Contains contaminant aluminum.[3] See Comments section for additional information on aluminum toxicity.)
Suitable diluents	D–LR, D–R, D–S, D5LR, D5NS, D5W, D10W, D20W, LR, NS, ½NS, or R.[9]
Maximum concentration	**Peripheral IV:** Generally, 40 mEq/L; however, concentrations up to 80 mEq/L may be required during severe hypokalemia.[3] Phlebitis is concentration related. **Central venous line:** ≤200 mEq/L.[13]

Potassium Chloride

Preparation and delivery	**Preparation:** Must be diluted prior to administration. The addition of concentrated potassium solution to a maintenance fluid requires careful mixing including inversion, agitation, and kneading of the container to insure a uniform potassium concentration throughout the fluid. Inadequate mixing may result in inconsistent potassium concentrations in the solution and deliver potassium at a rate that may exceed recommendations.[3,13] **Delivery system issues:** Potassium chloride injection 80 mEq/L added to dextrose 5% contained in glass bottles results in a leaching of precipitates consisting of silica and alumina.[14] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Contraindicated.[3]
Intermittent infusion	Must be diluted prior to administration.[3] ≤0.5–1 mEq/kg/hr and all sources should be considered.[4–8]
Continuous infusion	Usual route of administration as a component of maintenance fluids.
Other routes of administration	Contraindicated.[3]
Comments	**Precautions:** Use with caution in patients with renal and/or cardiac disease and in patients receiving digoxin and medications that can increase serum potassium concentration.[3] Aluminum may reach toxic concentrations following prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk due to kidney immaturity and their concurrent need for large amounts of calcium and phosphate solutions, which also contain aluminum.[15,16] Patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4–5 mcg/kg/day accumulate aluminum at levels associated with CNS and bone toxicity.[3,15] **Monitoring:** Clinical status, including urine output and periodic laboratory, should be monitored during therapy.[3] ECG monitoring should accompany infusion of individual doses >0.5 mEq/kg/hr.[3] **Miscellaneous:** In *adults*, the addition of lidocaine (50 mg/65 mL of infusate) decreased the pain associated with infusion.[17]

Potassium Phosphates

Brand names	Various manufacturers
Medication error potential	High-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. Potassium phosphates have been confused with potassium chloride and sodium phosphates, and patient harm did not occur.[2]
Contraindications and warnings	Administration of potassium at excessive rates may result in fatal dysrhythmias.[3] ECG monitoring should accompany high-dose potassium infusions.
Infusion-related cautions	Potassium infusions may cause phlebitis, which is concentration related. Extravasation may cause tissue sloughing and necrosis.[4] (See Appendix E for management of extravasation.) Potassium phosphates should not be administered with calcium-containing solutions.[5]
Dosage	Potassium phosphates are used to replace phosphate and not to replace potassium. The valence of phosphate changes with pH; therefore, the preferred units in which to express the amount of phosphate are mmol.[3] 4.4 mEq of potassium = 3 mmol of phosphate.[3,5] **Daily PN requirements (see Comments section)** **Neonates and infants:** 1–2 mmol/kg/day. Phosphate dosing is linked to calcium dosing. In neonates, the appropriate ratio is 2.5 mEq calcium:1 mmol of phosphates. The ratio gradually decreases to 1:1 as the infant approaches childhood.[6,7] **Older infants and children:** 0.5–1 mmol/kg/day. **Older children and adolescents:** 15 mmol/L or per 1000 kilocalories. **Diabetic ketoacidosis:** If the phosphate concentration is low, one-third to one-half the potassium deficit can be replaced as phosphates.[8] These patients should be monitored for hypocalcemia and hypomagnesemia.[8,9] **Hypophosphatemia in critically ill *adults* receiving PN**[10,11] **Mild (serum phosphate concentration of 2.3–3 mg/dL):** 0.16–0.32 mmol/kg over 4–6 hours. **Moderate (1.6–2.2 mg/dL):** 0.32–0.64 mmol/kg over 4–6 hours. **Severe (<1.5 mg/dL):** 0.64–1 mmol/kg over 8–12 hours.
Dosage adjustment in organ dysfunction	Potassium and phosphate ions are renally eliminated; therefore, extreme caution is required when dosing patients with renal insufficiency.[3]
Maximum dosage	Infants receiving PN may require daily doses of up to 2 mmol/kg for optimal bone growth.[6,7]
Additives	Contains contaminant aluminum.[3]
Suitable diluents	D–LR, D–R, D–S, D5LR, D5NS, D5W, D10W, LR, NS, ½NS, or R.[5]

Potassium Phosphates

Maximum concentration	**Peripheral IV:** 40 mEq potassium/L = 27 mmol phosphates/L.
Preparation and delivery	Must be diluted prior to administration.[3] Concentrated potassium solution addition to a maintenance fluid requires careful mixing including inversion, agitation, and kneading of the container to insure a uniform potassium concentration throughout the fluid. Inadequate mixing may result in inconsistent potassium concentrations in the solution and deliver potassium at a rate that may exceed recommendations. **Compatibility:** Compatibility with calcium is limited and depends on the calcium concentration, pH, and temperature of the final solution. (See Appendix D for PN compatibility information.) In compounding PN solutions, extreme care must be taken when calcium and phosphates are added to the same solution. Order of addition is critically important.
IV push	Contraindicated.[3]
Intermittent infusion	In *adults* the dose has been diluted in 100 or 150 mL of NS or D5W and infused over 4–6 hours (mild/moderate hypophosphatemia) or over 8–12 hours (severe hypophosphatemia).[10,11] The final potassium concentration of the solution should be considered.
Continuous infusion	Usual route of administration as a component of maintenance fluids or PN.[10,11]
Other routes of administration	Contraindicated.[3]
Comments	**Precautions:** Due to potassium content, use with caution in patients with renal and/or cardiac disease and in patients receiving digoxin and medications that can increase serum potassium concentration.[3] **Monitoring:** Administration of large amounts of phosphate may cause hypocalcemia.[3,6] Clinical status, including urine output, and periodic laboratory should be monitored during therapy.[3] Cardiac monitoring for high-dose potassium infusions.[3] **Miscellaneous:** Sodium phosphate is preferred as the phosphate source in pediatric PN because it contains less contaminant aluminum.

Pralidoxime Chloride (2-PAM Chloride)

Brand names	Protopam Chloride
Medication error potential	None reported.
Contraindications and warnings	**Contraindications:** In those with a known hypersensitivity to the drug.[1] **Warnings:** Should not be used for phosphorous, inorganic phosphate, or organophosphate poisoning not associated with anticholinesterase activity or in the case of carbamate class pesticide poisoning (may increase toxicity of carbaryl).[1] Use with caution in patients with myasthenia gravis because drug may precipitate a myasthenic crisis.[1]
Infusion-related cautions	Side effects (e.g., tachycardia, laryngospasm, and muscle rigidity) may be more common after rapid IV administration of doses larger than 30 mg/kg.[1,2] Weakness, blurred vision, dizziness, headache, nausea, and tachycardia have also been noted during infusion.[1]
Dosage	Most effective if administered within 24–48 hours of exposure, but patients presenting late (i.e., 2–6 days) may still benefit for use.[3,4] Should be administered in combination with atropine[1]; however, atropinization (e.g., flushing, mydriasis, tachycardia, dryness of the mouth and nose) may occur earlier than expected when compared to the used of atropine alone. This is especially true if the total dose of atropine has been large and the administration of pralidoxime chloride has been delayed. **Chemical warfare:** The dose and route of administration are based on severity of symptoms and treatment setting. In the *outpatient setting* (usually given IM) administer 15 mg/kg if mild-to-moderate symptoms are present. If the patient has severe symptoms give 25 mg/kg. In the ED give 15 mg/kg as slow IV injection for both mild-to-moderate or severe symptoms.[1] **Mild-to-moderate symptoms:** Blurred vision, sore eyes, teary eyes*, runny nose*, increased salivation such as sudden drooling*, chest tightness or difficulty breathing, tremors throughout the body or muscular twitching, nausea and vomiting, and involuntary respiratory secretions.[1] **Severe symptoms:** Strange or confused behavior, severe difficulty breathing or respiratory secretions, severe muscular twitching and general weakness**, involuntary urination and defecation*, convulsions, and unconsciousness.[1] * *These symptoms are less reliable as they can be observed in healthy infants and young children. Symptoms must be considered collectively when nerve agent or pesticide exposure is known or suspected.* ** *Infants may become drowsy or unconscious, with muscle floppiness rather than muscle twitching, soon after exposure to nerve agents or pesticides.* **Organophosphate poisoning:** For CNS and nicotinic (e.g., fasciculation, muscle weakness, paralysis, and decreased respiratory effort) symptoms. An IV loading dose followed by a continuous infusion may maintain therapeutic concentrations longer than traditional intermittent administration.[1] **Intermittent dosing:** 25–50 mg/kg, up to 2 g/dose, over 15–30 minutes; repeat dose after 1–2 hours and then q 6–12 hr if cholinergic signs recur.[1,3–5] **Continuous infusion:** An IV loading dose of 25–50 mg/kg infused over 15–30 minutes followed by a continuous infusion of 10–20 mg/kg/hr for ≤60 hours while symptoms persist.[1,2,6] A loading dose of 50 mg/kg may be more appropriate in patients with severe organophosphate poisoning.[1,6]

Pralidoxime Chloride (2-PAM Chloride)

Dosage adjustment in organ dysfunction	Should be used with caution and in reduced dosage in patients with renal dysfunction.[1]
Maximum dosage	As much as 2 g/dose,[1] 12 g in 24 hours,[3] and 0.5 g/hr by continuous infusion[7] have been used in *adults*, with the total dosage titrated according to cholinergic signs and clinical symptoms.
Additives	The autoinjector contains benzyl alcohol 20 mg/mL.[8] (See Appendix C for information related to toxicity.)
Suitable diluents	SW, NS. Diluents should be preservative-free due to larger volume required.[1]
Maximum concentration	50 mg/mL.[1]
Preparation and delivery	SW is used for reconstitution. NS is used for further dilution.[1] **Stability:** A MARK I autoinjector that was stored properly for 3 years beyond its expiration date appeared to be chemically stable.[9] Small amounts of degradation product were found in solubilized 2-PAM (autoinjector); however, it is unclear whether this may be a toxic by-product.[9]
IV push	20 mg/mL over at least 5 minutes in children.[1,4] In fluid-restricted patients, 50 mg/mL may be used.[6] Not to exceed 200 mg/min in *adults*.[1] (See Infusion-Related Cautions section.)
Intermittent infusion	Over 15–30 minutes.[1]
Continuous infusion	Loading dose followed by continuous IV infusion may maintain therapeutic concentrations longer than traditional short intermittent infusion therapy.[1]
Other routes of administration	May be given IM or SC when IV administration is not possible.[1] IM dose should be administered in the anterolateral aspect of the thigh to avoid the nerve, artery, vein and the femur.[1] May produce mild pain at the IM injection site 40–60 minutes after administration.[1]
Comments	Elevations in liver enzymes have been noted in volunteers receiving IM pralidoxime. Levels returned to normal in about 2 weeks.[1] **Drug interactions:** Concomitant administration of pralidoxime may increase side effects of atropine.[3,6] Morphine, theophylline, aminophylline, and succinylcholine are contraindicated in patients with anticholinesterase poisoning.[3,6] **Other:** Pralidoxime has been given for up to 22 days following poisoning with highly lipophilic organophosphates.[3]

Procainamide HCl

Brand names	Pronestyl
Medication error potential	High-alert medication associated with an increased risk of significant patient harm if an error occurs.[1] Look-alike, sound-alike drug names. May be confused with probenecid.[2] The abbreviation PCA may be mistaken for "patient-controlled analgesia" and should not be used.[3]
Contraindications and warnings	**U.S. boxed warning:** Potentially fatal blood dyscrasias have occurred with normal doses. Long-term administration leads to the development of a positive antinuclear antibody test in 50% of patients, which may result in a drug-induced, lupus erythematosus-like syndrome in 20% to 30% of patients.[3] **Contraindications:** Should not be used in patients with a known hypersensitivity to procainamide. Complete heart block; second- or third-degree heart block without pacemaker; torsades de pointes (twisting of the points), an unusual ventricular tachycardia; pre-existing QT prolongation; myasthenia gravis; or systemic lupus erythematosus.[3]
Infusion-related cautions	To avoid significant hypotension, limit the infusion rate to 20–30 mg/min.[3] Hypotension, atrioventricular block, cardiac dysrhythmias, and cardiac arrest may occur.[3]
Dosage	Monitor ECG. If QRS widens >50% or if the patient develops hypotension during the loading dose, the infusion should be discontinued and the maintenance dose held until signs of toxicity resolve.[4] **Tachycardia:** Supraventricular tachycardia unresponsive to vagal maneuvers and adenosine; wide-complex ventricular tachycardia unresponsive to synchronized cardioversion or adenosine.[4] **Neonates:** 7–10 mg/kg over 60 minutes followed by 20–80 mcg/kg/min.[5–7] Dose required to achieve therapeutic serum concentrations is similar to that of older infants and children; however, doses may need to be reduced in premature infants.[6] **Infants and children** **Loading dose:** 2–5 mg/kg (maximum 100 mg) over 5 minutes.[3,8] May be repeated q 5–10 min until the arrhythmia is controlled to a maximum of 15 mg/kg (500 mg) in 30 minutes[3,8] or 10–15 mg/kg over 30–60 minutes followed by maintenance infusion.[4] **Maintenance dose:** 20–120 mcg/kg/min[3,4,8–10] to a maximum of 2 g in 24 hours[8] or 50–100 mg/kg/day divided q 4 hr.[8]
Dosage adjustment in organ dysfunction	If CrCl is 10–50 mL/min/1.73 m^2, decrease dose by 33%[5] or give normal dose q 6–12 hr[9]; if <10 mL/min, decrease dose by 67%[5] or give q 8–24 hr.[9]
Maximum dosage	17 mg/kg/dose in *adults*.[4] 2 g/day IV[3,4] and 4 g/day IM.[3,4]
Additives	Each mL contains 1 mg of methylparaben and sodium metabisulfate.[10] (See Appendix C for specific information about sulfite hypersensitivity.)

Procainamide HCl

Suitable diluents	D5W, NS, or SW.[10]
Maximum concentration	20–30 mg/mL for loading doses[10] or 4 mg/mL for intermittent infusions.[10]
Preparation and delivery	**Stability:** Store at room temperature. The colorless solution may turn slightly yellow upon standing or refrigerator. Injection of air into the vial causes the solution to darken. Solutions darker than light amber should be discarded. Variable stability has been reported in dextrose containing solutions with significant drug loss in as little as 4 hours.[10]
IV push	20–30 mg/mL over 5–10 minutes at a maximum infusion rate of 20–30 mg/min (50 mg/min in *adults*).[3,4] Severe hypotension may occur with rapid administration.
Intermittent infusion	2–4 mg/mL concentration solution over 25–30 minutes.[4,10]
Continuous infusion	2 or 4 mg/mL for continuous infusion preferably in NS or SW.[10]
Other routes of administration	Has been given IM and IO.[4] IM dose of 20–30 mg/kg/day divided q 4–6 hr (maximum of 4 g/day).[5]
Comments	**Monitoring:** Because large variability exists in patient response to initial and maintenance doses, individualize dosage based on serum concentration and clinical response. Reference range for procainamide is 4–10 mg/L and for combination of procainamide plus n-acetyl procainamide is 5–30 mg/L.[3,11] **Drug interactions:** Procainamide is primarily metabolized by CYP2D6.[3] Because it is associated with numerous pharmacokinetic and pharmacodynamic drug–drug interactions,[12] consult appropriate resources for dosing recommendations before combining any drug with procainamide.

Promethazine HCl

Brand names	Phenergan, Phenazine, Promethegan, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that promethazine has been confused with perphenazine, phenazopyridine and prednisone; no patient harm resulted.[2] USP also reports that promethazine has been confused with Compazine and prochlorperazine; patient harm resulted.[2] USP reports that Phenergan has been confused with Compazine, phenobarbital, and phenylephrine; no patient harm resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** A black box warning was added to prescribing information as follows[3]: Promethazine is contraindicated in pediatric patients <2 years of age because of the potential for fatal respiratory depression. Postmarketing cases of respiratory depression, including fatalities, have been reported with promethazine use in patients <2 years of age. A wide range of weight-based doses have resulted in respiratory depression in these patients. Caution should be exercised when administering promethazine to pediatric patients >2 years of age. Use the lowest effective dose and avoid the use of concomitant therapy with respiratory depressants. Injection of promethazine may cause severe chemical irritation and damage to tissues, regardless of the route of administration. Irritation and tissue necrosis can also result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration.[3] **Contraindications:** Contraindicated in patients <2 years of age, in comatose states, and in patients with a previous hypersensitivity to the drug.[3] **Other warnings:** Promethazine use may result in CNS depression, respiratory depression, bone marrow depression, neuroleptic malignant syndrome, and lower seizure threshold.[3] Use caution in patients with risk of QTc prolongation.[4]
Infusion-related cautions	Tissue irritation and damage can occur from promethazine injection regardless of the route of administration.[3] Extravasation may cause tissue necrosis.[3,5,6] In an effort to increase awareness of the risk of severe tissue injury with IV promethazine administration, the Institute for Safe Medication Practices has recommended that institutions only stock the concentration of 25 mg/mL, limit doses used, further dilute the concentration of 25 mg/mL prior to administration, use large veins for administration, administer via a running IV at the furthest port from the patient, and administer slowly.[7] Intra-arterial injection may result in gangrene of the affected extremity.[3,6]
Dosage	**Antiemetic/sedation** **Children >2 years of age:** 0.25–1 mg/kg (not to exceed 25 mg) q 4–6 hr PRN.[8–10]
Dosage adjustment in organ dysfunction	No dosage adjustment required in *adult* patients with renal dysfunction. May cause excessive sedation in end-stage renal disease.[11]

Promethazine HCl

Maximum dosage	The dose should not exceed half of the suggested *adult* dose or up to 25 mg/dose in children or 50 mg/dose in adolescents.[3]
Additives	Each mL of solution (25 mg/mL and 50 mg/mL) contains 0.1 mg disodium edetate, 0.04 mg calcium chloride, 0.25 mg sodium metabisulfite, and 5 mg phenol.[10] See Appendix C for more specific information about potential adverse effects of sulfites.
Suitable diluents	NS, ½NS, D2.5W, D5W, D10W, LR, R, D–LR combinations, D–R combinations, D-saline combinations.[12]
Maximum concentration	25 mg/mL.[3,12]
Preparation and delivery	See Appendix D for PN compatibility information.
IV push	≤25 mg/mL; administer into tubing of a compatible infusion fluid at a rate <25 mg/min.[3,10] Administer through large bore vein or through a running IV line. Consider administering over 10–15 minutes.[13]
Intermittent infusion	No information available to support administration by this method.
Continuous infusion	No information available to support administration by this method.
Other routes of administration	≤25 mg/mL via deep IM injection is the preferred route of administration.[3] SC injection is contraindicated.[3,5]
Comments	**Significant adverse effects:** All FDA-reported cases of serious adverse events (respiratory depression, apnea, cardiac arrest, dystonias, CNS effects, seizures, neuroleptic malignant syndrome) in children (0 to 16 years of age) were evaluated.[14] Respiratory depression occurred in 22 patients (1.5 months to 2 years of age) and seven of these patients died. A wide range of doses was represented (0.45–6.4 mg/kg). Nine patients received ≤1 mg/kg in addition to another drug with respiratory depressant effects.[14] Excessively large doses of antihistamines may cause hallucinations, convulsions, and sudden death in infants and children. Acutely ill children who are dehydrated may be more susceptible to dystonias. For these reasons, antiemetics are not recommended for the treatment of uncomplicated vomiting in children; their use should be limited to prolonged vomiting of unknown etiology.[3] **Laboratory interference:** An increase in blood glucose and false–positive or false–negative pregnancy tests (diagnostic tests utilizing human chorionic gonadotropin [hCG] and anti-hCG) may occur with promethazine therapy.[3] **Other:** Meperidine, promethazine, and chlorpromazine have been used in combination (Demerol, Phenergan, Thorazine [DPT] cocktail) to sedate pediatric patients.[8,9,15–18] However, with the availability of safer and more effective agents,[16,19,20] this combination is no longer recommended.[18] Steroid-induced psychosis in a 32-month-old child with acute graft-versus-host disease post bone marrow transplant resolved with promethazine (0.5 mg/kg) therapy.[21]

Propofol

Brand names	Diprivan 1% (generic)
Medication error potential	High-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. Confusion has been reported for Diprivan, Ditropan, and Diprivan with Diflucan and Ditropan.[2,3] Confusion also noted between propofol with propranolol.[3]
Contraindications and warnings	**Contraindications:** Known hypersensitivity to DIPRIVAN Injectable Emulsion or its components (i.e., eggs, soybean). Has been associated with fatal and life-threatening anaphylaxis.[4] Should not be used when general anesthesia or sedation are contraindicated.[4] **Warnings:** Should only be administered by persons trained in general anesthesia, who are not involved in the conduct of the surgical/diagnostic procedure, and who are trained in cardiovascular resuscitation and airway management.[4] Patients should be continuously monitored in a facility where maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation are immediately available. Propofol has been associated with the propofol-related infusion syndrome (PRIS) when used for sedation in pediatric and *adult* patients admitted to the ICU. The syndrome, which has resulted in death, is characterized by severe metabolic acidosis, hyperkalemia, lipemia, rhabdomyolysis, hepatomegaly, and cardiac and renal failure. Although prolonged administration of more than 4 mg/kg/hr for greater than 48 hours increases the likelihood, the syndrome has also been reported with large-dose, short-term infusions during surgical anesthesia.[4] (See Rare Adverse Effects in the Comments section.) The emulsion is not an antimicrobially preserved product under USP standards; hence, it can support the growth of microorganisms.[4] Failure to use aseptic technique can cause microbial contamination and subsequent fever, infection/sepsis, and/or death. Unused portions should be discarded as directed within the required time limits.[4]
Infusion-related cautions	Transient pain has been noted in 45% of pediatric patients when a small vein of the hand is used without lidocaine pretreatment.[4] This can be reduced to <10% when pretreated with lidocaine (1 mL of a 1% solution; not to exceed 20 mg lidocaine per 200 mg propofol) or when the antecubital veins is used.[5] Cardiorespiratory depression has occurred during bolus dosing or after rapid increase in the dosage rate.[4] Assess the patient frequently and wait 3–5 minutes between dosage adjustments.[4] Abrupt discontinuance of propofol may cause flushing of the hands and feet, agitation, tremors, hyperirritability, bradycardia, agitation, or jitteriness.[4]
Dosage	**Anesthesia:** *Not recommended for the induction of anesthesia in patients <3 years of age and for the maintenance of anesthesia in patients <2 months of age*.[4] **Induction doses (3 years of age):** Mean dose 2.5 mg/kg (range: 1–4 mg/kg) given over 20–30 seconds until onset of induction.[4,6–14] Noncommunicative and nonverbal children with cerebral palsy require less propofol than healthy children.[15] Those older than 16 years should be given 40 mg (2–2.5 mg/kg) q 10 sec until onset of induction.[4] *Adults* >16 years who have a neurosurgical diagnosis should receive smaller doses (i.e., 20 mg [1–2 mg/kg] q 10 sec).[4] **Maintenance (2 months of age):** If clinical signs of light anesthesia are not present after 30 minutes, the infusion rate should be decreased.[4] Doses have ranged from 133 to 400 mcg/kg/min.[11,12,16] During clinical trials mean doses were 125–300 mcg/kg/min (7.5–18 mg/kg/hr).[4] Those >16 years received 100–200 mcg/kg/min (6–12 mg/kg/hr) or 40 mg (2–2.5 mg/kg) q 10 sec.[4] Younger children may require larger doses. (See Rare Adverse Effects in the Comments section.)

Dosage *(cont.)*	**Epilepsy (refractory status epilepticus):** Use in refractory status is based on nonrandomized studies and case reports; hence, it should be used cautiously. Initial loading doses of 3 mg/kg followed by continuous infusion of 40–300 mcg/kg/min (2.4–18 mg/kg/hr) for up to 48 hours have been used in patients from 9 months to 19 years.[17–20] (See Rare Adverse Effects in the Comments section.) **Procedural sedation:** 0.5–3 mg/kg initially followed by 50–200 mcg/kg/min (3–12 mg/kg/hr)[21–23] with additional boluses of 1 mg/kg PRN.[21,23] For the initial bolus, one group used 2.5 mg/kg in children and 3 mg/kg in infants.[23] As an alternative to continuous infusion, boluses of 0.2 to ≤1 mg/kg have been used PRN for patient comfort.[21,24] **Sedation:** Propofol lacks approved labeling for sedation in critically ill, mechanically-ventilated pediatric patients.[4] Given the current controversy regarding the PRIS, the lowest effective dose should be used and the dose should not exceed 4 mg/kg/hr.[25] The infusion rate should be increased by 5–10 mcg/kg/min (0.3–0.6 mg/kg/hr) until the desired effect is achieved.[4] A minimum period of 5 minutes should be allowed for peak effect between titration events.[4] The patient should be switched to a benzodiazepine (i.e., midazolam or lorazepam) if adequate sedation cannot be achieved with dose of 4 mg/kg/hr or if prolonged therapy (≥48 hours) is required.[25] While on propofol, the patient should be monitored for clinical features and laboratory findings that have been attributed to the syndrome. Should symptoms occur propofol should be discontinued. (See Rare Adverse Effects in the Comments section.)
Dosage adjustment in organ dysfunction	No adjustment in hepatic or renal dysfunction.[4,26]
Maximum dosage	Not established. (See Rare Adverse Effects in the Comments section.)
Additives	The generic formulation may contain either sodium metabisulfite or benzyl alcohol. (See Appendix C for specific information about sulfite hypersensitivity.) Each mL of Diprivan contains 100 mg soybean oil, 22.5 mg glycerol, 12 mg egg lecithin, and disodium edetate 0.005%. NaOH is used to adjust pH.[4,27] The generic contains 100 mg soybean oil, 22.5 mg glycerol, 12 mg egg yolk phospholipid, and 0.25 mg sodium metabisulfite. NaOH is used to adjust pH.[27] Patients who are allergic to eggs and/or soybean products should not be given propofol.[4] A 14-month-old patient with a history of egg and peanut allergies developed anaphylaxis after receiving propofol.[28] Refer to package insert to identify which preservative (EDTA, sodium metabisulfite, or benzyl alcohol) the product contains.
Suitable diluents	If dilution is required, dilute with D5W to a concentration no less than 2 mg/mL.[4]
Maximum concentration	10 mg/mL.[4]
Preparation and delivery	**Delivery system issues:** To ensure proper delivery of propofol, in-line IV filters should be >5 microns.[4] Do not administer through the same IV catheter with blood or plasma. Tubing and any unused portions of propofol vials should be discarded after 12 hours. **Stability:** Store between 4°C to 22°C.[4] Do not freeze. If used directly from vial/prefilled syringe, use within 12 hours after vial has been spiked.[4] Several incidences of bacterial contamination have been reported following repackaging[29] or improper storage of propofol[30] and Intralipid.[31] If propofol is transferred to a syringe or other container, the transfer should be done as soon as the vial is opened and the product should be discarded and administration lines changed after 6 hours.[4] Shake well before use. Do not use if emulsion has separated. **Compatibility:** See Appendix D for PN compatibility information.

Propofol

IV push	10 mg/mL[4] given over 20–30 seconds.[4,7–10,13] Has been given safely over 10 seconds.[9]
Intermittent infusion	Not routinely used.
Continuous infusion	2–10 mg/mL in D5W.[4] Do not dilute <2 mg/mL due to emulsion instability.[4]
Other routes of administration	IM not recommended.[4]

Comments

Rare adverse effects: PRIS is associated with a variety of symptoms, including progressive metabolic acidosis, lipemia, hypotension, multisystem organ failure, and rhabdomyolysis, which may culminate in cardiovascular collapse.[25] Several practitioners have successfully managed PRIS with venovenous hemodiafiltration and charcoal hemofiltration or extracorporeal membrane oxygenation.[25] Plasmapheresis was not beneficial.[25]

Acute dystonia and seizures have also been reported in those with and without a history of epilepsy.[32–36] Subtherapeutic doses or abrupt withdrawal may contribute to this effect; hence, increasing the dose may terminate seizure activity.

Acute pancreatitis has been reported.[37–39]

A 9-month-old who received large doses of propofol for 5 days for status epilepticus developed first and secondary degree atrioventricular block, widened QRS, and ventricular tachycardia.[40]

Monitoring: Arterial blood gases, potassium, creatine phosphokinase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), BUN, and creatinine. Serum triglyceride levels should be obtained prior to initiation of therapy and every 3–7 days thereafter, especially if receiving for >48 hours with doses exceeding 50 mcg/kg/min.[41] Collect blood from IV port opposite to the site of propofol infusion or temporarily suspend infusion and flush port prior to blood draw.

Drug interactions: Propofol is a substrate of CYP2C9 and 2B6 (major) and a minor substrate for CYP1A2, 2A6, 2C19, 2D6, 2E1, and 3A4.[41] It inhibits CYP3A4 (major), CYP1A2 and 2C19 (moderate), and 2C9, 2D6 (weak).[41] In pediatric patients, administration of fentanyl concomitantly with DIPRIVAN Injectable Emulsion may result in serious bradycardia.[4] Consult appropriate resources for dosing recommendations before combining any drug with propofol.

Other: Diprivan contains EDTA an antimicrobial agent. Although rare, at large doses (2–3 g/day), EDTA may be toxic to the renal tubules.[4] In those predisposed to renal impairment, urinalysis and urine sediment should be assessed prior to initiation and on alternate days during therapy.[4] EDTA may bind to zinc. Although this formulation has not been associated with decreased zinc levels or zinc deficiency-related adverse events, it should not be infused for longer than 5 days without providing a drug-free period.[4]

Propranolol HCl

Brand names	Inderal
Medication error potential	High-alert medication (adrenergic agonist) that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. Confusion has been reported between Inderal and Adderall,[2,3] and between Inderal and Enduron, Imdur, Imuran, Inderide, Isordil, and Toradol.[2] *Significant differences exist between oral and IV dosing. Use caution when converting from one route of administration to another.*
Contraindications and warnings	**U.S. boxed warning:** Abrupt withdrawal in patients with coronary artery disease may exacerbate angina or precipitate myocardial infarction; hence, propranolol should be gradually discontinued over about 2 weeks.[4] **Contraindications:** Propranolol is contraindicated in cardiogenic shock; sinus bradycardia and greater than first-degree block; bronchial asthma; and known hypersensitivity to propranolol.[4] Also, propranolol should not be used in patients with hyperactive airway disease, chronic obstructive pulmonary disease, and Raynaud syndrome. **Other warnings:** Use cautiously in patients with diabetes mellitus as propranolol may block hypoglycemia-induced tachycardia and blood pressure changes.[4] Acute elevations in blood pressure have been reported after insulin-induced hypoglycemia.[4] Beta blockers may aggravate arterial insufficiency and should be used with caution in those with peripheral vascular disease.[4] Patients with a history of anaphylactic reactions may be more reactive to a repeated allergen challenge and may not respond to doses of epinephrine used to treat an allergic reaction.[4]
Infusion-related cautions	Rapid administration may cause hypotension and cardiac standstill.[4,5]
Dosage	*Significant differences exist between oral and IV dosing. Use caution when converting from one route of administration to another.* **Arrhythmias:** 0.01–0.25 mg/kg (maximum dose 1 mg) over 10 minutes[6–9] not to exceed 1 mg/min.[4] Repeat dose every 2 minutes.[6,7] (See Maximum Dosage section.) **Burn patients:** 0.5–1 mg/kg q 4–8 hr for 5–10 days.[10–12] Used to decrease heart rate, cardiac work, and metabolic stress associated with severe burn. **Hypertensive emergency:** IV labetalol is the preferred beta blocker.[13,14] **Infundibular spasm ("Tet" spell):** Oxygen should be given before propranolol.[15] 0.01–0.02 mg/kg over 10 minutes and titrate to effect (up to 0.1–0.2 mg/kg/dose).[16–18] May repeat dose in 15 minutes.[17,18] Maximum initial dose is 1 mg.[17] One study suggests staring doses of 0.15–0.25 mg/kg/dose infused over 10 minutes followed by one repeat dose if needed.[15]
Dosage adjustment in organ dysfunction	No adjustment in renal dysfunction.[19] Use cautiously in hepatic dysfunction and consider dosage reduction.
Maximum dosage	0.2 mg/kg,[7,16] not to exceed 1 mg as initial dose for infants.[4,6,16] Although the AAP recommends a maximum initial dose in children of 10 mg,[6] the usual dose for *adults* is 1–3 mg.[4]

Propranolol HCl

Additives	None reported.
Suitable diluents	D5W, NS, D5NS, D5½NS, ½NS, LR.[20]
Maximum concentration	1 mg/mL.[20]
Preparation and delivery	**Stability:** Store at room temperature and protect from freezing or excessive heat. Maximum stability at a pH of 3 with rapid decomposition at alkaline pH.[20] **Compatibility:** Incompatible with bicarbonate.[20] **Photosensitivity:** Protect from light.[20]
IV push	Not recommended.[4]
Intermittent infusion	1 mg/mL[20] administered over 10 minutes.[4,6] Not to exceed 1 mg/min.[4]
Continuous infusion	Not used.
Other routes of administration	None reported.
Comments	**Monitoring:** ECG, blood pressure, and heart rate should be monitored during IV administration.[21] **Drug interactions:** Propranolol is primarily metabolized by CYP1A2, CYP2D6, and to a lesser extent by CYP2C19 and CYP3A4.[4] Mild inhibitor of CYP1A2 and CYP2D6.[4] **Pharmacodynamic considerations:** Caution should be exercised when administering propranolol with drugs that slow atrioventricular nodal conduction (e.g., digitalis, lidocaine, and calcium channel blockers).[4] **Other:** IV propranolol was successfully used to treat a 9-year-old girl with catecholaminergic polymorphic ventricular tachycardia, a rare genetic disorder.[22]

Protamine Sulfate

Brand names

Generic

Medication error potential

Look-alike, sound-alike drug names.

ISMP reports that protamine sulfate has been confused with Protonix.[1] USP reports that protamine sulfate has been confused with ProAmatine, protirelin, and Protonix.[2]

Contraindications and warnings

U.S. boxed warning: Protamine sulfate can cause severe hypotension, cardiovascular collapse, noncardiogenic pulmonary edema, catastrophic pulmonary vasoconstriction, and pulmonary hypertension. Appropriate facilities and supportive measures including resuscitative equipment and medications should be readily available in case of a severe reaction.[3]

Risk factors include high dose, overdose, rapid administration, repeated doses, previous administration of protamine, and current or previous use of protamine-containing drugs. Allergy to fish, previous vasectomy, severe left ventricular dysfunction, and abnormal preoperative pulmonary hemodynamics may be risk factors. The risk to benefit should be considered in these patients.[3]

Protamine sulfate should not be given when bleeding unrelated to heparin occurs.[3]

Infusion-related cautions

See U.S. Boxed Warning in the Contraindications and Warnings section.

In two case reports, doses of 3 and 4.5 mg/kg after cardiopulmonary bypass resulted in an anaphylactoid response in a 6- and a 2.5-year-old child, respectively.[4,5] Whether or not either child had any risk factors for this reaction was not clear.

Dosage

Heparin: 1 mg of protamine sulfate will neutralize about 100 USP heparin units.[3,6] Because heparin's half-life is short, over time less protamine is required. Only one-half the dose of protamine should be used if IV heparin has been discontinued for 30 minutes Individual doses should not exceed 50 mg.[3,6] (See Comments section.)

The following doses have been recommended for pediatric patients following IV injection of heparin[6]:

Time Since Last Heparin Dose Received	Protamine Dose Ratio (mg of protamine/100 units of heparin received in the previous 2 hr)
<30 min	1 mg
30–60 min	0.5–0.75 mg
60–120 min	0.375–0.5 mg
>120 min	0.25–0.375 mg

If the heparin was administered by deep SC injection, 1–1.5 mg protamine/100 USP heparin units should be used. As an example, part of the dose (i.e., 25–50 mg) can be given over 10 minutes followed by an infusion of the remaining calculated dose over 8–16 hours.[7]

Low molecular weight heparin (LMWH)[7]

Time (hr) Since Last LMWH Dose Received	Protamine Dose Ratio (mg of protamine/100 anti-factor Xa units of LMWH given [mg protamine/1 mg enoxaparin or dalteparin])
<8 hr, first protamine dose	1 mg
<8 hr, second protamine dose (if aPTT remains elevated 2–4 hr after first protamine dose)	0.5 mg
8–12 hr	0.5 mg
>12 hr	May not be necessary

Protamine Sulfate

Dosage adjustment in organ dysfunction	None noted.
Maximum dosage	50 mg.[3,6]
Additives	Contains 9 mg NaCl/10 mg protamine.[3]
Suitable diluents	D5W, NS.[3,8]
Maximum concentration	10 mg/mL.[3]
Preparation and delivery	**Compatibility:** A manufacturer states that protamine sulfate is incompatible with certain antibiotics, including several of the cephalosporins, and penicillins.[3]
IV push	Contraindicated. Rapid administration may result in hypotension, bradycardia, pulmonary hypertension, etc.[3,6]
Intermittent infusion	Infuse dose (maximum 50 mg) over 10 minutes[3,6] and ≤5 mg/min.[3,6]
Continuous infusion	Not indicated.
Other routes of administration	Not indicated.
Comments	Note that the USP adopted new manufacturing controls for heparin. Beginning October 8, 2009, the reference standard for heparin products changed to the World Health Organization's International Standards (IS) unit dose definition. This is about 10% less potent than the previous USP unit.[9] **Adverse effects:** Following cardiopulmonary bypass (CPB), a 6-week-old infant experienced pulmonary hypertension and impending respiratory failure immediately after receiving protamine.[10] This infant was treated with high-frequency oscillation ventilation, inhaled nitric oxide (iNO), and prostacyclin and recovered. Following CPB, a 3-year-old child developed pulmonary hypertension after protamine was given.[11] She failed to respond to conventional treatments and was started on iNO after which the pulmonary artery pressures decreased. She was subsequently weaned from iNO and mechanical ventilation and was discharged on postoperative day 4. One study in *adults* reported that when given prior to protamine, IV famotidine, but not diphenhydramine, prevented hypotension.[12] **Monitoring:** Coagulation studies including activated partial thromboplastin time or activated clotting time should help to guide therapy. Blood pressure should be monitored during infusion.[3,6]

Protein C Concentrate (Human)

Brand names	Ceprotin
Medication error potential	None reported by ISMP or USP.[1–3]
Contraindications and warnings	Protein C concentrate is made from human plasma. While the risk of transmission of infectious agents is low, the product may still transmit disease.[4] Consider vaccination for hepatitis A and B in patients receiving repeated doses of protein C concentrate.[4] Concurrent administration with tPA or other anticoagulants may increase bleeding risk.[4] Protein C concentrate contains heparin: if heparin-induced thrombocytopenia is suspected, discontinue.[4] Contains sodium >200 mg. Patients with renal impairment or on a low-sodium diet should be informed.[4]
Infusion-related cautions	The drug product may contain traces of mouse protein and/or heparin. If allergic/hypersensitivity symptoms occur, the infusion should be discontinued.[4]
Dosage	Dosage regimen (dose, frequency, duration) should be tailored to individual patient based on severity of protein C deficiency, age, patient's clinical condition, and protein C plasma concentrations.[4–5] The manufacturer reports that pediatric patients from 2 days of age to adolescence have been included in retrospective and prospective trials.[4] In general, dosing recommendations for pediatric patients and *adults* are as follows: **Acute episodes/short-term prophylaxis[4–5]** **Initial dose:** 100–120 International Units/kg. **Subsequent 3 doses:** 60–80 International Units/kg q 6 hr. **Maintenance dose:** 45–60 International Units/kg q 6–12 hr. **Long-term prophylaxis[4–5]:** 45–60 International Units/kg q 12 hr. After the initial dose, subsequent doses should be adjusted to maintain peak protein C plasma activity of 100%. After the acute episode has subsided, continue same dose to maintain trough protein C plasma activity above 25%.[4–5] **Purpura fulminans secondary to meningococcemia[6–7]** **Neonates:** 100 International Units/kg/day divided q 4–6 hr. **Infants, children, adolescents:** 100–150 International Units/kg q 6 hr for 72 hours, then 50–150 International Units/kg q 12 hr until target symptom resolution or 7 days of treatment.
Dosage adjustment in organ dysfunction	No information is known regarding dosage adjustment in organ dysfunction.[4]
Maximum dosage	In clinical trials, doses up to 600 International Units/kg/day (i.e., 150 International Units/kg q 6 hr) for acute episodes/short-term prophylaxis and 291.7 International Units/kg/day for long-term prophylaxis have been used.[4]
Additives	Contains 8 mg/mL human albumin and 8.8 mg/mL sodium; thus, the total sodium content in the maximum daily dose is greater than 200 mg.[4] Monitor patients on a low sodium diet and/or with renal impairment closely.[4] Contains heparin; if heparin-induced thrombocytopenia is suspected, check platelets and discontinue therapy.[4]

Protein C Concentrate (Human)

Suitable diluents	SW.[4]
Maximum concentration	100 International Units/mL.[4]
Preparation and delivery	Product available in 500 International Units/vial and 1000 International Units/vial to be reconstituted with 5 mL and 10 mL SW, respectively (final concentration of 100 International Units/mL). Filter with filter needle provided prior to administration. Dose should be given within 3 hours of reconstitution.[4]
IV push	Not indicated.
Intermittent infusion	For patients ≥10 kg, infuse at 2 mL/min; for pediatric patients <10 kg, do not exceed an infusion rate of 0.2 mL/kg/min.[4]
Continuous infusion	An initial dose of 100 International Units/kg followed by continuous IV infusion with initial rate of 10 International Units/kg/hr adjusted daily to keep plasma protein C concentration 80–120 International Units/mL has been used for purpura fulminans.[8]
Other routes of administration	SC infusions have been used in two children with severe protein C deficiency at doses of 250–350 International Units/kg to maintain trough protein C levels of >25 International Units/dL.[9]

Ranitidine

Brand names	Zantac, generic
Medication error potential	Look-alike, sound-alike drug names. ISMP reports that Zantac has been confused with Xanax and Zyrtec.[1] USP reports that Zantac has been confused with Xanax, Zocor, Zofran, and Zyrtec and that ranitidine has been confused with loratadine, nizatidine, and rimantadine.[2]
Contraindications and warnings	Known hypersensitivity to the drug.[3]
Infusion-related cautions	Bradycardia has been reported with rapid administration.[3] Infusion of 50 mg over <5 minutes has resulted in transient hypotension in critically ill *adults*.[4] Pain at the injection site (IV and IM administration) may occur. Burning and itching may also occur with IV administration.[3]
Dosage	**Active GI bleeding, peptic ulcer disease, or hypersecretory conditions:** 0.5–5 mg/kg/day given in divided doses or via continuous infusion.[5–7] **Prophylaxis against dexamethasone-associated ulceration in premature infants with bronchopulmonary dysplasia:** 0.031–0.125 mg/kg/hr during dexamethasone therapy.[8] An infusion of 0.0625 mg/kg/hr was sufficient to increase and maintain gastric pH >4.[8] **Prophylaxis against stress ulceration** **Premature neonates:** 0.5 mg/kg q 12 hr.[9] **Term neonates:** Although one study recommended 1.5 mg/kg q 8 hr,[9] another study reported that term neonates receiving 2 mg/kg/dose did not require dosing more frequently than q 12 hr.[10] Ranitidine has also been given as a loading dose of 2 mg/kg over 10 minutes followed by 0.083 mg/kg/hr.[10] **Extracorporeal membrane oxygenation:** 2 mg/kg/dose q 12–24 hr or as a continuous infusion.[3] **Infants and children:** 2–4 mg/kg/day is routinely recommended.[3] Although doses of 1–6 mg/kg/day divided q 6–8 hr have been used,[11–14] it has been suggested that critically ill infants and children require larger doses (i.e., >3 mg/kg/day) and more frequent dosing.[14–16] Alternatively, a loading dose of 0.15–0.6 mg/kg[5,6,14,17] over 15 minutes followed by a continuous infusion of 0.031–0.25 mg/kg/hr has been used.[5,7,8,12–14,18–20]
Dosage adjustment in organ dysfunction	Adjust dosage in patients with severe renal dysfunction.[3,21] **CrCl 30–50 mL/min:** 1 mg/kg q 12 hr.[21] **CrCl 10–29 mL/min:** 0.5 mg/kg q 12 hr.[21] **CrCl <10 mL/min:** 0.5 mg/kg q 24 hr.[21] Supplement doses above for hemodialysis and peritoneal dialysis (0.5 mg/kg q 24 hr) and continuous renal replacement therapy (1 mg/kg q 12 hr).[21]
Maximum dosage	200 mg/day in infants and children and 400 mg/day in *adults*.[3] 2.5 mg/kg/hr and infusion rates of 220 mg/hr have been used in *adults* with hypersecretory conditions.[3]

Ranitidine

Additives	Each mL of the premixed solution (50 mg/50 mL) contains 4.5 mg NaCl.[3]
Suitable diluents	D5W, D10W, LR, NS, or sodium bicarbonate 5%.[3]
Maximum concentration	2.5 mg/mL for IV and 25 mg/mL for IM administration.[3,22]
Preparation and delivery	Visually compatible with PN[22] and stable in PN and TNA solutions for 24 hours at room temperature.[23–25] (See Appendix D for additional PN compatibility information.)
IV push	Not recommended because of risk of bradycardia and hypotension.[4] Dilute to ≤2.5 mg/mL in D5W, D10W, LR, or NS and inject over at least 5 minutes,[3,22] not to exceed 4 mL/min (10 mg/min).[3,22]
Intermittent infusion	May give via intermittent infusion (≤0.5 mg/mL); infuse at 5–7 mL/min (15–20 minutes).[3,22]
Continuous infusion	May give via continuous infusion (<0.5 mg/mL).[3,22]
Other routes of administration	May give IM (25 mg/mL).[3,22]
Comments	**Significant adverse effects:** Bradycardia began 2 hours after ranitidine was infused in a neonate and gradually resolved within 24 hours of discontinuation.[26] No other cause of bradycardia could be determined. Ranitidine has produced a negative chronotropic effect in children receiving concomitant tolazoline.[27] **Rare adverse effects:** May precipitate acute porphyric attacks; do not use in patients with a history of acute porphyria.[3] **Monitoring:** Increases in alanine aminotransferase (ALT) may occur when given at higher doses for 5 days or more; monitor ALT beginning at day 5 of therapy.[3] **Drug interactions:** Ranitidine inhibits a variety of CYP isoenzymes and is associated with numerous drug interactions.[3] Consult appropriate resources for dosing recommendations before combining any drug with ranitidine. **Pharmacodynamic considerations:** Several critically ill children have failed to respond to 6 mg/kg/day.[12,16] Tolerance developed in five of six infants who received continuous infusion ranitidine in PN solutions for 2–6 weeks.[18] **Laboratory interference:** May result in a false–positive urine protein test; testing with sulfosalicylic acid recommended.[3] **Other:** H2-blocker therapy has been associated with the incidence of necrotizing enterocolitis in very low birth weight infants.[28,29]

Rasburicase

Brand names	Elitek
Medication error potential	None known.
Contraindications and warnings	**U.S. boxed warning:** May cause life-threatening anaphylaxis, hemolysis, methemoglobinemia.[1,2] Interference with uric acid assessment due to uric acid degradation may also occur.[1,2] (See Laboratory Interference in the Comments section.) **Contraindications:** Patients with a known hypersensitivity to rasburicase or any components, past or known history of hemolytic reactions to drug or any components, and glucose-6-phosphatase dehydrogenase (G6PD) deficiencies.[1,2] (See Significant Adverse Effects in the Comments section.) **Other warnings:** Patients should receive concurrent hydration.[1]
Infusion-related cautions	Hypersensitivity reactions have been reported.[3] (See Dosage section.) Give concomitant IV hydration.[1] Anaphylaxis may occur at any point during infusion. Immediately and permanently discontinue rasburicase should anaphylaxis occur.[1]
Dosage	Indicated for the initial management of plasma uric acid levels in pediatric patients who are expected to develop tumor lysis syndrome and subsequent elevations in uric acid as a result of their disease (lymphoma, leukemia, and solid tumor malignancies) and/or treatment regimen.[1] Rasburicase may elicit an antibody response that may increase hypersensitivity reactions and decrease efficacy.[3] For this reason, the manufacturer recommends that it should be used for a single course of therapy only.[1] Rasburicase has been administered safely and effectively to pediatric and *adult* patients who had received prior therapy.[3,4] **Hyperuricemia:** 0.101–0.2 mg/kg/day for up to 5–7 days.[1–10] Chemotherapy should begin 4–24 hours after administration of rasburicase.[1] Some trials have given 0.15–0.2 mg/kg q 12 hr for the first 48–72 hours in patients at greatest risk of developing hyperuricemia.[3,4,6–9] A single dose of 0.15 mg/kg was effective at decreasing uric acid levels in patients (18 months to 72 years) with bulky tumor.[11] A single dose of 6 mg has been found to be effective in *adults*.[12]
Dosage adjustment in organ dysfunction	Not established.
Maximum dosage	0.2 mg/kg/dose or 0.4 mg/kg/day.[1]
Additives	None.
Suitable diluents	Reconstitute with diluents supplied.
Maximum concentration	Not established. Desired dose of reconstituted rasburicase should be added to NS for a final total volume of 50 mL.[1]

Rasburicase

Preparation and delivery	**Preparation:** Using aseptic technique and syringes of appropriate volume, remove the predetermined dose of rasburicase from the reconstituted vials and inject into an infusion bag containing the appropriate volume of NS to achieve a final total volume of 50 mL.[1] Do not shake or vortex vial once reconstituted.[1] **Delivery:** Do not filter infusion. A separate line is preferred. Flushing the line with 15 mL of NS before and after administration is also acceptable.[1] Final solution for injection should be infused over 30 minutes.[1]
IV push	Rasburicase should not be administered as a bolus injection.[1–2]
Intermittent infusion	Dilute rasburicase vials with 1 mL of provided diluent and add desired rasburicase dose to an infusion bag of NS for a final volume of 50 mL to be infused over 30 minutes.[1] Total dosing volumes of 10–50 mL have been given to infants.[7]
Continuous infusion	No information available to support administration by this method.
Other routes of administration	No information available to support administration by other routes.

Rifampin

Brand names	Rifadin IV
Medication error potential	ISMP's *Confused Drug Names* lists confusion between Rifadin and Rifater.[1] USP reports confusion with ribavirin, rifabutin, and rifaximin.[2] Likewise, confusion between Rifadin and rifabutin and Rifamate.[2]
Contraindications and warnings	**Contraindications:** Rifampin is contraindicated in patients with a history of hypersensitivity to any of the rifamycins.[3] **Warnings:** May cause hepatic dysfunction.[3,4] Fatalities have occurred in patients with liver disease and in patients concurrently taking other hepatotoxic agents. Hyperbilirubinemia can also occur early in therapy.[3] An isolated, moderate rise in bilirubin and/or transaminases is not an indication for interrupting treatment. The decision should be predicated on the results of repeat tests and the patient's clinical condition. Discontinue if signs of hepatocellular damage are noted.[3] (See Monitoring in the Comments section.) Rifampin may induce delta amino levulinic acid synthetase and can exacerbate porphyria.[3]
Infusion-related cautions	Extravasation may cause local irritation and inflammation.[3]
Dosage	Should not to be used for the treatment of meningococcal disease as rapid resistance may develop.[3] **Neonates:** 10–20 mg/kg/day divided q 12 hr.[5,6] **Infants and children:** 10–20 mg/kg/day divided q 12 hr[7,8] or given as a single dose q 24 hr.[8] One study in children concluded that it may be more appropriate to shorten the dosing interval from 12 hours to 8 hours after 2 days of therapy to avoid prolonged periods of low plasma concentrations.[9] **Prophylaxis of intraventricular shunt revision:** 20 mg/kg as a single dose 1 hour prior to surgery.[10]
Dosage adjustment in organ dysfunction	No adjustment in renal.[11]
Maximum dosage	20 mg/kg/day[3] not to exceed 600 mg/day.[3]
Additives	None.
Suitable diluents	D5W, NS.[3,12]
Maximum concentration	≤6 mg/mL.[3,12]
Preparation and delivery	**Stability:** Infusion solution should be administered within 4 hours of preparation because rifampin may precipitate.[3]
IV push	Not recommended.[3]

Intermittent infusion	Over 30 minutes or 3 hours.[3,12]
Continuous infusion	Not used.
Other routes of administration	IM and SC not recommended.[3,12] Intraventricular administration (5 mg/dose) has been used in cases of CNS tuberculosis.[13]

Comments

Rare adverse effects: Thrombocytopenia has been reported.[3] It is generally associated with large dose intermittent therapy, but has also been reported after resumption of interrupted treatment.[3] Although it resolves if drug is stopped at the first appearance of purpura, cerebral hemorrhage and fatalities have been reported when rifampin is continued.[3]

Cutaneous reactions (e.g., of flushing and itching with or without a rash) are mild and self-limiting.[3] Although serious hypersensitivity associated cutaneous reactions have been reported (e.g., pruritus, urticaria, rash, pemphigoid reaction, erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, eosinophilia, sore mouth, sore tongue, and conjunctivitis), anaphylaxis is rare.[3]

Monitoring: Monitor hepatic transaminases at baseline and then every 2–4 weeks during therapy in patients with hepatic dysfunction or receiving hepatotoxic drugs.[3] The manufacturer notes that baseline tests are unnecessary in pediatric patients unless a complicating condition is known or suspected.[3]

Drug interactions: Rifampin induces CYP isozymes to cause numerous drug interactions. Consult appropriate resources before combining any drug with rifampin.[14]

Laboratory interference: Rifampin may interfere with standard microbiological assays for serum folate and vitamin B_{12}.[3] Cross-reactivity and false–positive urine screening tests for opiates have been reported.[3] Reduced biliary excretion of contrast media used for visualization of the gallbladder requires that tests be performed before the morning dose of rifampin.[3]

Other: May discolor body secretions (e.g., sweat, urine, and tears).[3]

RiTUXimab

Brand names	Rituxan
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP and USP report that riTUXimab has been confused with InFLIXimab; patient harm resulted.[2,3] USP reports that Rituxan has been confused with riTUXimab; no patient harm resulted.[3]
Contraindications and warnings	**U.S. boxed warning:** RiTUXimab carries black box warnings for fatal infusion reactions (see Infusion-Related Cautions section), tumor lysis syndrome, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy.[4] Tumor lysis syndrome (hyperkalemia, hypocalcemia, hyperuricemia, hyperphosphatemia, and acute renal failure) necessitating dialysis to prevent renal failure has been reported within 12–24 hours after the first riTUXimab infusion in patients with non-Hodgkin lymphoma. Treatment should include supportive care with electrolyte correction and dialysis, as needed. Prophylaxis may be warranted in patients with a high tumor burden. Severe mucocutaneous reactions with fatal outcomes have been reported 1–13 weeks after the initial riTUXimab dosage.[4] **Other warnings:** May cause hepatitis B reactivation, increased risk of infection, life-threatening cardiac arrhythmias, renal toxicity, bowel obstruction, and bowel perforation.[4]
Infusion-related cautions	RiTUXimab has been associated with the development of a fatal infusion reaction complex (hypoxia, pulmonary infiltrates, respiratory distress, myocardial infarction, ventricular fibrillation or cardiogenic shock). This complex most commonly occurs with the first dose.[4] Severe infusion reactions (hypotension, hypoxia, bronchospasm, or angioedema) are most common with the first dose and generally occur within 30–120 minutes after beginning the infusion. Treatment should include interruption of the infusion and the use of supportive care measures, including oxygen, epinephrine, corticosteroids, bronchodilators, and IV fluids. Often the infusion can be resumed with a 50% reduction in the infusion rate. Close monitoring in subsequent courses should occur.[4] Other less serious hypersensitivity reactions are common and can be treated with a 50% reduction in infusion rate and acetaminophen and diphenhydramine. Bronchodilators and IV saline may also be used as needed.[4] Premedication with acetaminophen and diphenhydramine is recommended to reduce the incidence of hypersensitivity reactions (e.g., fevers, chills, rigors).[4]
Dosage	Consult institutional protocols for complete dosing information. RiTUXimab is part of combination therapy to treat newly diagnosed, relapsed, or refractory CD20 positive B-cell, non-Hodgkin lymphoma, or B-cell acute lymphoblastic leukemia (ALL), as well as other hematologic disorders. **CD20 positive B-cell, non-Hodgkin lymphoma** **Initial:** 375 mg/m^2 once weekly for 4–8 doses as monotherapy or in combination with CHOP (i.e., **C**yclophosphamide, **H**ydroxydaunorubicin [doxorubicin], **O**ncovin [vincristine], and **P**rednisone or prednisolone).[4–7]

Dosage *(cont.)*	**Retreatment:** 375 mg/m^2 once weekly for 4 doses or once weekly for 4 doses given q 6 mo for up to 2 years.[4,7] **Refractory:** 375 mg/m^2 on days 1 and 3 in combination with ifosfamide, mesna, carboplatin, and etoposide.[8] **B-cell ALL:** 375 mg/m^2 to conventional salvage therapy.[9] **Relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma:** 250 mg/m^2 administered 4 hours prior to Indium-111 ibritumomab; 7–9 days later, 250 mg/m^2 administered within 4 hours of Yttrium-90 ibritumomab.[4,10] **Post-transplant lymphoproliferative disorder:** 375 mg/m^2 once weekly for 3–4 doses.[11,12] **Autoimmune hemolytic anemia:** 375 mg/m^2 once weekly for 2–4 doses.[13,14] **Chronic idiopathic thrombocytopenic purpura:** 375 mg/m^2 once weekly for 4 doses.[15,16] **Refractory systemic lupus erythematosus:** 375 mg/m^2 once weekly for 2–4 doses or 750 mg/m^2 on days 1 and 15 (max dose 1000 mg).[17] **Refractory severe nephrotic syndrome**: 375 mg/m^2 once weekly for 1–4 doses.[18–20]
Dosage adjustment in organ dysfunction	Not established.
Maximum dosage	Clinical trials have reported single dosages up to 500 mg/m^2.[4]
Additives	Contains 9 mg/mL NaCl.[4]
Suitable diluents	D5W or NS.[4]
Maximum concentration	4 mg/mL.[4]
Preparation and delivery	Do not mix or dilute with other drugs.[4]
IV push	Not recommended.[4]
Intermittent infusion	Dilute with suitable diluent to final concentration of 1–4 mg/mL and infuse at a beginning rate of 50 mg/hr. If no hypersensitivity reactions occur, the rate may be escalated by 50 mg/hr q 30 min to a maximum rate of 400 mg/hr. In patients tolerating the first infusion, subsequent cycles may begin at a rate of 100 mg/hr, escalating up to a maximum rate of 400 mg/hr.[4]
Continuous infusion	No information available to support administration by this method.
Other routes of administration	No information available to support administration by other routes.

RiTUXimab

Comments

Significant drug interactions: Avoid concomitant use with other immunosuppressants and monoclonal antibodies (e.g. pimecrolimus, abciximab, natalizumab). Avoid use of live vaccines for at least 3 months after therapy. Therapeutic effects of inactivated vaccines may be diminished.[4,22]

Significant adverse effects: RiTUXimab is associated with a minimal (<10%) risk of emesis.[21] Generally, prophylaxis for acute and delayed emesis is not needed.

Monitoring: CBC with platelets, cardiac and renal function, fluid balance, and vital signs.[4,22]

Antihypertensive medications should be held for 12 hours prior to infusion.[4,22]

Rocuronium Bromide

Brand names	Zemuron, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that rocuronium has been confused with Romazicon and vecuronium; no patient harm resulted. USP also reports that Zemuron has been confused with vecuronium; patient death resulted.[2]
Contraindications and warnings	**Contraindications:** Hypersensitivity to rocuronium or any of its components.[3] In one study, 69% of patients with confirmed rocuronium allergy demonstrated cross-sensitivity to vecuronium.[4] **Warnings:** Use carefully under the supervision of experienced clinicians; personnel should be skilled in airway management, resuscitation, and respiratory support. Intubation and ventilatory support equipment, including oxygen therapy, should be readily available. Reversal agents should be readily available when giving rocuronium.[3]
Infusion-related cautions	Hypersensitivity reactions, hypotension, arrhythmias, bronchospasm, and severe anaphylaxis (life-threatening in some cases) have been reported but appear to be rare.[3]
Dosage	*Respiratory function must be supported during use of this agent. Concurrent administration of a sedative is also necessary. Monitoring of neuromuscular transmission with a peripheral nerve stimulator is recommended during continuous infusion or with repeated dosing.*[3,5] **Dosing adjustment for obesity:** The manufacturer recommends that the dose (0.6 mg/kg) should be based on actual body weight, not ideal or lean body mass.[3] However, two studies in morbidly obese *adults* found that doses of 1.2 mg/kg[6] and 0.6 mg/kg[7] based on ideal body weight provided clinically acceptable intubating conditions for surgery. When administered with inhalational anesthetics, such as halothane, isoflurane, or sevoflurane, the dose of rocuronium should be reduced by 20% to 50%.[8,9] (See individual dosing sections.) **Induction and maintenance of neuromuscular blockade** **Neonates:** 0.5–1.2 mg/kg for nonemergent intubation.[10,11] **Infants:** 0.3–0.6 mg/kg repeated q 20–30 min PRN to maintain pharmacological paralysis.[3,11–14] AAP recommends 1 mg/kg for intubation.[15] May follow a bolus dose with a continuous infusion of 0.3–0.8 mg/kg/hr (5–13 mcg/kg/min).[3,9,16] Maintenance doses during halothane anesthesia are 0.075–0.125 mg/kg, and during sevoflurane/isoflurane anesthesia are 0.15 mg/kg PRN.[3] **Children:** 0.4–0.8 mg/kg repeated q 20–30 min PRN to maintain pharmacological paralysis.[3,12–14,17] May follow a bolus dose with a continuous infusion of 0.3–0.8 mg/kg/hr (5–13 mcg/kg/min).[3,9,16] (See Comments section.) Maintenance doses during halothane anesthesia are 0.075–0.125 mg/kg, and during sevoflurane/isoflurane anesthesia are 0.15 mg/kg.[3]
Dosage adjustment in organ dysfunction	An increased initial dosage may be required for complete neuromuscular blockade in patients with hepatic impairment.[3] Duration of neuromuscular blockade in these patients may also be prolonged.[3] No dosage adjustment required in those with renal impairment.[3] In children with renal failure who were older than 1 year of age, a single bolus dose did not cause prolonged neuromuscular blockade but was associated with a slower onset of action than that noted in healthy children.[18]

Rocuronium Bromide

Maximum dosage	Bolus doses as high as 2 mg/kg,[13] and continuous infusions up to 2.2 mg/kg/hr (37 mcg/kg/min)[16] have been reported.
Additives	None.
Suitable diluents	D5W, D5NS, NS, LR.[3,19]
Maximum concentration	10 mg/mL for IV push; 5 mg/mL for infusion.[3]
Preparation and delivery	Rocuronium is an acidic solution; do not administer with alkaline solutions.[3]
IV push	10 mg/mL over 5 seconds.[3]
Intermittent infusion	Not administered by this method.
Continuous infusion	0.5–1 mg/mL recommended.[20] The manufacturer provides information for continuous infusion with a solution of 0.5, 1, and 5 mg/mL.[3]
Other routes of administration	Not recommended by manufacturer.[3] Although a single IM dose of 1 mg/kg in infants and 1.8 mg/kg in children has been used,[21] rocuronium should not be used as an alternative to IM succinylcholine when rapid intubation is necessary. The use of IM administration is not recommended since it does not consistently provide satisfactory tracheal intubating conditions.[21] When given in the deltoid muscle of infants and children, serum concentrations peak at 13 minutes, with about 80% of the dose absorbed systemically.[22]
Comments	**Other:** For neonatal nonemergent intubations, AAP recommends that vagolytic and muscle relaxant agents should be considered and that analgesic agents or anesthetic doses of a hypnotic agent should be administered. Rocuronium or vecuronium is preferred over other available neuromuscular blocking agents.[10] **Trials comparing rocuronium doses in patients receiving concomitant anesthetics for intubation prior to surgery:** In children undergoing tonsillectomy with propofol and alfentanil anesthesia, lower-dose rocuronium (0.45 mg/kg) produced good intubating conditions, a shorter recovery time, but a slightly prolonged onset of action compared to 0.6 mg/kg rocuronium or 0.1 mg/kg of vecuronium.[23] Conversely, in children undergoing elective surgery with halothane anesthesia, rocuronium 0.45 mg/kg was inferior to 0.6 mg/kg for producing satisfactory intubating conditions.[17] In children 4–8 years old undergoing elective surgery, rocuronium 0.6 mg/kg with propofol 2.5 mg/kg provided acceptable intubating conditions.[24] **Significant adverse effects:** Prolonged neuromuscular blockade may occur. Factors that potentiate the duration of neuromuscular blockade include acidosis, hypokalemia, hypermagnesemia, neuromuscular disease, hepatic disease, and other medications.[3,12] (See Drug Interactions below.) Patients with neurological diseases, such as myasthenia gravis, may exhibit increased sensitivity.[3] One case report describes an 18-year-old with Kugelberg-Welander syndrome (a type III spinal muscular atrophy) undergoing elective surgery. A single dose of rocuronium 25 mg (0.83 mg/kg) along with general anesthesia facilitated intubation.[25] Decreased sensitivity to rocuronium may occur in patients with severe burns, muscle trauma, demyelinating lesions, neuropathy, or infection.[3]

Rocuronium Bromide

Comments *(cont.)*

Drug interactions: Concomitant administration of other drugs (e.g., aminoglycosides, inhalational anesthetics, magnesium, succinylcholine, vancomycin) may prolong neuromuscular blockade.[3] Consult appropriate resources for additional information on drug interactions.

In children with cerebral palsy undergoing orthopedic surgery, total rocuronium requirements were reduced by adding magnesium sulfate 50 mg/kg bolus followed by 15 mg/kg/hr.[26]

Ropivacaine HCl

Brand names	Naropin
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that ropivacaine has been confused with bupivacaine; no patient harm resulted.[2]
Contraindications and warnings	**Contraindications:** Ropivacaine is contraindicated in patients with known hypersensitivity to the drug or any amide anesthetic.[3] **Warnings:** Ropivacaine should only be administered by persons specifically trained in the use of local anesthetics.[3] The FDA notified healthcare professionals in November 2009 of the risk of chondrolysis following continuous intra-articular infusion of local anesthetics, including ropivacaine, via elastomeric infusion devices. The FDA has received 35 reports of chondrolysis; some were in previously healthy young *adults,* and most following shoulder surgery. The cases had received the local anesthetics for postoperative pain for periods of 48–72 hours. Chondrolysis symptoms (joint pain, stiffness, loss of motion) occurred as early as 2 (median 5) months following therapy with the local anesthetic.[3,4]
Infusion-related cautions	*Not for IV infusion or IM administration. Administer only by lumbar epidural injection or infusion, by thoracic epidural infusion, by injection for nerve block, and by infiltration*.[3] Accidental IV injection may result in cardiac arrhythmia or cardiac arrest, seizures, coma, and respiratory arrest.[3,5] Oxygen, CPR, intubation equipment, medications, and trained personnel in emergency management should be immediately available when using ropivacaine.[3]
Dosage	Dose varies with the anesthetic procedure, the area to be anesthetized, the vascularity of the tissues, the number of neuronal segments to be blocked, the depth and duration of anesthesia required, as well as individual response. A test dose of epinephrine with or without lidocaine has been used to verify that the needle is not in the vascular space.[3,6,7] Once the catheter is placed, negative aspiration of blood or cerebrospinal fluid[3,8–11] and the absence of cardiovascular changes following a test dose indicates correct position of the catheter.[3,11,12] (See Significant Adverse Effects in the Comments section.) The manufacturer does not recommend the use of ropivacaine in pediatric patients.[3] **Caudal/epidural block:** Children 1.25–6.5 mg/kg[6,8,9,11–14] or 1 mL/kg of 0.2% solution.[5] **Epidural continuous infusion** **Children 4 months to 7 years:** A loading dose of 1–1.4 mg/kg followed by 0.2–0.4 mg/kg/hr for 48 hours.[10,13] One group of investigators reported continuous infusion up to 96 hours without adverse events.[10] **Children from 7–12 years:** Twenty-four children assigned to receive a patient-controlled epidural infusion consisting of bolus doses of 4 mg (lockout 10 minutes) with a continuous infusion of 3.2 mg/hr (total hourly ropivacaine could equal 27.2 mg, if needed) required less drug than 24 children assigned to receive a continuous epidural infusion of 0.4 mg/kg/hr (239 mg/48 hr compared to 576 mg/48 hr, respectively).[7]

Dosage *(cont.)*	***Adults*:** A loading dose of 10–14 mg (5–7 mL of 0.2% solution) followed by 12–28 mg/hr (6–14 mL/hr of 0.2% solution) for up to 72 hours.[3] **Local anesthesia:** 16 children ages 9.9 ± 2.9 years undergoing maxillar alveolar grafting received 0.4–0.8 mg/kg followed by 0.2 mg/kg/hr through a catheter positioned at an iliac crest donor site for up to 48 hr for postoperative analgesia.[15]
Dosage adjustment in organ dysfunction	Use with caution in patients with hepatic, renal, or cardiovascular disease.[3,5]
Maximum dosage	Not established.
Additives	None.
Suitable diluents	Not diluted.
Maximum concentration	1% (10 mg/mL).[3,16]
Preparation and delivery	Should not be mixed with alkaline solutions as precipitation is likely to occur.[3]
IV push	Do not administer IV.[3,5] (See Infusion-Related Cautions section.)
Intermittent infusion	Do not administer IV.[3,8,12] (See Infusion-Related Cautions section.) 1 mg/kg over 10 minutes has been administered via epidural catheter.[10]
Continuous infusion	Do not administer IV. (See Infusion-Related Cautions section.) For epidural infusion only.[3,5,7,10,13] (See Dosage section.)
Other routes of administration	Do not administer IM.[3] (See Infusion-Related Cautions section.)
Comments	**Significant adverse effects:** Systemic absorption of local anesthetics may result in toxic plasma concentrations, resulting in cardiovascular adverse effects, including decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, and cardiac arrest. Patients should be carefully monitored during injection. Use with caution in patients with underlying cardiovascular disease.[3,5] Persistent hiccups have been reported in a term neonate who received a continuous epidural infusion of fentanyl with ropivacaine 0.23–0.32 mg/kg/hr for postoperative analgesia following tracheoesophageal fistula repair. The hiccups resolved after discontinuing ropivacaine.[17] **Drug interactions:** Patients receiving class III antiarrhythmics (e.g., amiodarone) may be at increased risk for cardiac adverse effects.[3] Ropivacaine and its primary metabolite are metabolized via the CYP1A2 isoenzyme. Concomitant use of CYP1A2 inhibitors may be associated with the potential for serious drug interactions.[3] Consult appropriate resources for dosing recommendations before combining any drug with ropivacaine.

Sargramostim

Brand names

Leukine; yeast derived (*Saccharomyces cerevisiae*) recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF)

Medication error potential

Look-alike, sound-alike drug names.

USP reports that sargramostim has been confused with filgrastim and Sandostatin.[1]

Contraindications and warnings

Contraindications: Patients with ≥10% leukemic myeloid blasts in bone marrow or peripheral blood; patients with known hypersensitivity to GM-CSF, products derived from yeast, or any product component; 24 hours before or after chemotherapy or radiotherapy treatment.[2]

Warnings: Allergic reactions have been reported. Should this occur, discontinue the infusion and institute appropriate therapy.[2]

Neonates should not receive liquid or lyophilized sargramostim reconstituted with BW due to the presence of benzyl alcohol.[2]

Infusion-related cautions

A first-dose response that includes respiratory distress, hypotension, tachycardia, and flushing is common with infusion of the first dose of a cycle and usually resolves with treatment.[2] This does not recur with subsequent doses in the cycle.[2]

Dosage

The products derived from *Escherichia coli* and Chinese hamster ovaries are not available in the United States. Some of the studies cited evaluated these products, which may have different potencies, specific activities, and adverse effects.

Neutropenia

Postchemotherapy neutropenia: 250–1000 mcg/m^2/day IV over 2 hours for up to 14 days[2–4] or 5 mcg/kg/day IV (bacteria [*Escherichia coli*] derived) over 4 hours for up to 21 days.[5] Alternatively, 5 mcg/kg/day SC for up to 21 days following chemotherapy or irradiation.[6,7] (See Comments section.)

Bone marrow transplantation: 250 mcg/m^2/day IV over 2 hours beginning 2–4 hours after transplant and not earlier than 24 hours after chemotherapy or after radiation until absolute neutrophil count (ANC) >1500 cells/mm^3 for 3 consecutive or for 21 days.[2] Alternatively, 250 mcg/m^2/day IV over 4 hours beginning after transplant for 21 days.[8]

Premature and term neonates (reconstitute lyophilized product in SW to avoid benzyl alcohol)

Neutropenia (≤31 weeks gestational age): 10 mcg/kg/day IV or SC × 5 days.[9]

Aplastic anemia: Nine children (0.7–19 years of age), received induction phase continuous infusion doses of either 8 mcg/kg/day increased after 14 days to 16 mcg/kg/day for up to 14 more days if the hematologic response was inadequate or doses of 16 mcg/kg/day increased to 32 mcg/kg/day (Chinese hamster ovary cell derived).[10] After the induction phase, administration was changed to SC dosing.[10] Eighteen children received a standard immunosuppressive regimen for 5 days and then GM-CSF at 250 mcg/m^2/day SC was started.[11]

Mobilization of peripheral blood progenitor cells (PBPC): 250 mcg/m^2/day IV over 24 hours or SC once daily, continued through the period of PBPC cell collection.[2]

Dosage adjustment in organ dysfunction

None. Patients with existing renal or hepatic impairment should have renal function or liver function monitored weekly.[2]

Maximum dosage

Not established. Some reports suggest 32 mcg/kg[12] or 1500 mcg/m^2.[3]

Sargramostim

Additives	The liquid product contains 1.1% benzyl alcohol, 40 mg/mL mannitol, 10 mg/mL sucrose, and 1.2 mg/mL tromethamine.[2] After reconstitution with BW or SW, each mL of the lyophilized product contains 40 mg mannitol, 10 mg sucrose, and 1.2 mg/mL tromethamine.[2] BW contains benzyl alcohol. See Appendix C for information about potential benzyl alcohol toxicity in neonates.
Suitable diluents	NS.[2]
Maximum concentration	250 (reconstituted lyophilized powder) or 500 mcg/mL (liquid).[2]
Preparation and delivery	An in-line membrane filter should not be used when sargramostim is given IV.[2] **Stability:** The lyophilized product reconstituted with SW must be used within 6 hours of reconstitution because it contains no preservatives.[2] If the final concentration will be <10 mcg/mL, albumin should be added to the NS diluent to achieve a final albumin concentration of 0.1% prior to the addition of sargramostim to prevent adsorption to the drug delivery system.[2] Add 1 mg albumin per mL of NS.[2] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Not indicated.[2]
Intermittent infusion	Usually infused over 2–4 hours.[2–4]
Continuous infusion	≥10 mcg/mL in NS.[2]
Other routes of administration	The liquid product (500 mcg/mL) can be given SC undiluted.[2] The lyophilized product is reconstituted to 250 mcg/mL and given SC without further dilution.[2] Not for IM administration.
Comments	The use of colony-stimulating factor decreased febrile neutropenia, length of hospitalization, and number of infectious episodes but did not shorten the duration of neutropenia nor lessen treatment delays in children with acute lymphocytic leukemia.[12] **Monitoring:** CBC with differential is recommended twice a week during therapy to evaluate for leukocytosis. If the ANC >20,000 cells/mm^3, or the platelet count >500,000 cells/mm^3, the dose should be decreased by 50% or held.[2] **Adverse effects:** Children receiving multiple courses of SC GM-CSF have experienced acute toxicities at various times during their dosing including fever, tachycardia, hypotension, and rash requiring discontinuation.[6] Sargramostim has the potential to activate the coagulation system in pediatric patients receiving bone marrow or stem cell transplant.[13] The severity of adverse reactions appears to be less with the yeast-derived product than those derived in Chinese hamster ovary cells or bacteria.[1] Pericardial and pleural effusions, myalgias, and volume overload are dose-limiting side effects in *adults*.[2] Although adverse effects have been reported in children, they are usually mild[4,5] and unrelated to dose.[3] However, cardiopulmonary symptoms occurred in a child receiving continuous infusion of 24 mcg/kg/day[10] and a deep vein thrombosis occurred in a child being treated for myelosuppressive chemotherapy, who inadvertently received 1500 mcg/m^2/day for 7 days.[3]

Sodium Bicarbonate

Brand names

Various manufacturers; available in concentrations of 0.5 mEq HCO_3/mL (4.2%), 0.6 mEq/mL (5%), 0.9 mEq/mL (7.5%), and 1 mEq/mL (8.4%)

Medication error potential

Look-alike, sound-alike drug names.

USP reports that sodium bicarbonate has been confused with sodium chloride and patient harm resulted.[1]

Contraindications and warnings

Contraindications: Ongoing chloride losses as in vomiting or GI suction; those receiving diuretics known to cause a hypochloremic alkalosis; hypocalcemia.[2]

Infusion-related cautions

Sodium bicarbonate should be infused slowly in neonates to decrease possible hypernatremia that may decrease cerebrospinal fluid, pressure and result in intracranial hemorrhage.[2–4] The manufacturer recommends an infusion rate not to exceed 0.33 mEq/kg/hr in infants and children up to 2 years of age to reduce the risk of intracranial hemorrhage.[2] However, in cardiac arrest, faster infusion rates may be warranted.[2]

Extravasation may cause local ischemia and tissue necrosis.[2] (See Appendix E for management of extravasation of concentrated products.)

Dosage

CPR: Sodium bicarbonate should only be used after establishment of airway and adequate ventilation.[5,6] Routine use of sodium bicarbonate does not improve the outcome of cardiac arrest in children; however, there are certain times when its use can be considered.[5,6] The 4.2% solution (0.5 mEq/mL) should be used in newborns and infants up to 2 years of age.[2,5]

Cardiac arrest: 1 mEq/kg followed by 0.5 mEq/kg q 10 min during continued arrest.[2]

Hyperkalemic cardiac arrest: 1 mEq/kg[6] up to 50 mEq/dose in *adults*.[7]

Cocaine-induced ventricular arrhythmia: 1–2 mEq/kg.[6]

Tricyclic antidepressant, sodium channel blocker toxicity: Boluses of 1–2 mEq/kg until arterial pH is >7.45; then use continuous infusion (150 mEq/L in D5W solution) to maintain alkalosis (arterial pH 7.45–7.55). In cases of severe intoxication, maintain arterial pH 7.50–7.55.[5,6]

Metabolic acidosis: Calculate the sodium bicarbonate dose using the following equations[2,8]:

HCO_3 (mEq) = 0.3 × weight (kg) × base deficit (mEq/L), or

HCO_3 (mEq) = 0.5 × weight (kg) × [24-serum HCO_3 (mEq/L)]

If laboratory measurements are not available: 2–5 mEq/kg administered over 4–8 hours. Subsequent doses should be individualized based on response and severity of metabolic acidosis.[2,8] Complete correction of the base deficit should occur over >24 hours because the compensatory response to changes in ventilation may be delayed.[2]

Diabetic ketoacidosis (DKA): Adjunctive bicarbonate (1–2 mEq/kg over 60 minutes) may be considered in children with severe DKA and a pH <6.9.[9,10] However, a retrospective study reported no difference in rate of metabolic recovery and complications between patients treated with or without bicarbonate, and hospitalization was prolonged in the bicarbonate group.[11] The administration of bicarbonate has also been associated with development of cerebral edema.[12]

Urinary alkalinization (See Comments section.)

Poisonings (salicylate) in children[13]**:** 25 mEq infused over 1 hour. Urine pH should be measured q 15–30 min and additional doses given until the urine pH is 7.5–8.5, then urine pH should be measured hourly. Potassium concentrations should be measured hourly. The arterial pH should be ≤7.5.

Sodium Bicarbonate

Dosage *(cont.)*	**Prevention of tumor lysis syndrome**[14]**:** D5¼NS with 50–100 mEq/L $NaHCO_3$ (no potassium) infused at 3–6 L/m^2/day and titrated to a urinary pH of 7–7.5. Serum HCO_3 concentration should be kept ≤30 mEq/L. An alternative strategy for urine alkalinization has been reported in 26 patients ages 15–25 years old receiving high-dose methotrexate without hyperhydration. These patients received 500 mEq sodium bicarbonate over 1 hour before the methotrexate dose on day 1, then again on days 2–4 of therapy. Urine pH remained above 7.5 in all patients.[15]
Dosage adjustment in organ dysfunction	Use with caution in patients with renal insufficiency, congestive heart failure, or in those with edema and sodium retention.[2]
Maximum dosage	2 mEq/kg/dose,[5] 8 mEq/kg/day in infants,[2,3] 2–5 mEq/kg as intermittent infusions over 4–8 hours.[2] Adolescents and young *adults* received 500 mEq over 1 hour as part of a hyperalkalinization regimen for high-dose methotrexate.[15]
Additives	Each gram of sodium bicarbonate provides 12 mEq sodium.[16] The 5% solution in 500-mL bottles also contains 0.9 mg/mL of edetate disodium.[16]
Suitable diluents	D5NS, D5W, D10W, D-LR, R.[16]
Maximum concentration	**Neonates and infants:** 4.2% (0.5 mEq/mL).[2] **>2 years:** 8.4% (1 mEq/mL).[2]
Preparation and delivery	**Compatibility:** Bicarbonate inactivates norepinephrine and dobutamine.[17] Adequately flush the IV lines between administration of resuscitation drugs and sodium bicarbonate.[6] Incompatible with calcium containing fluids.[2] See Appendix D for PN compatibility information.
IV push	This method of administration is indicated in cardiac arrest.[6] May administer over 5 minutes in *adults.*[7]
Intermittent infusion	2–5 mEq/kg over 4–8 hours in older children.[2]
Continuous infusion	May be given continuously. In nonemergent situations, rate should not exceed 0.33 mEq/kg/hr for infants and children up to 2 years of age to decrease risk of intracranial hemorrhage.[2]
Other routes of administration	May be administered IO if unable to establish adequate IV access during cardiac arrest.[6]
Comments	Urinary alkalinization and forced diuresis has been used to prevent acute renal failure due to rhabdomyolysis. However, a retrospective review of 1771 *adults* with rhabdomyolysis due to trauma who received bicarbonate and mannitol forced diuresis found that renal failure was not decreased when compared to a group that did not receive this treatment.[18]

Sodium Bicarbonate

Comments *(cont.)*

Monitoring: Electrolytes, including potassium and calcium, should be monitored.[2] Measurement of arterial pH (blood gas) is indicated during resuscitation. Potassium concentration and pH are inversely related; therefore, increases in pH result in a decrease in potassium concentration. Blood calcium binding to albumin is enhanced with alkalosis resulting in decreased ionized calcium. Urinary pH should be measured during urinary alkalinization.

Adverse effects: Rapid changes in serum sodium concentration should be avoided.[3,4] Metabolic alkalosis is a complication that may result in paradoxical CNS acidosis, hypokalemia, hypocalcemia, and impaired delivery of oxygen to the tissue.[9]

Sodium Chloride

Brand names	Various manufacturers 0.45% saline (½NS) = 77 mEq/L 0.9% saline (NS) = 154 mEq/L 3% saline = 513 mEq/L 5% saline = 855 mEq/L
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error (hypertonic solutions [greater than 0.9% saline]).[1] USP reports that sodium chloride has been confused with potassium chloride. Sodium chloride has been confused with sodium bicarbonate and patient harm resulted.[2] ISMP reports that use of hypotonic saline solutions postoperatively resulted in acute hyponatremia and death in two previously healthy children.[3]
Contraindications and warnings	A variety of sodium concentrations are available. The bulk packages are concentrated and are not intended for direct infusion.[4] Choose products carefully.
Infusion-related cautions	During chronic hyponatremia, shifts of water and sodium occur to maintain normal cellular volume in the brain.[5,6] Too rapid correction of hyponatremia can result in osmotic demyelination syndromes (central pontine myelinolysis; extrapontine myelinolysis).[5–10] Similarly, during chronic hypernatremia the brain generates idiogenic osmoles to maintain cerebral intracellular osmolality. Too rapid decreases in serum sodium may cause water to move into the brain cells resulting in cerebral edema, seizures, and coma.[5,6] In general, the serum sodium should not be increased or decreased ≥10–12 mEq/L per day in these chronic conditions.[5,6]
Dosage	**Maintenance IV fluids:** Isotonic (NS with dextrose) as opposed to hypotonic (0.18% or 0.45% NaCl with dextrose) fluids at maintenance rates reduced the incidence of hyponatremia in surgical[11] and in nonsurgical[12] pediatric patients; however, one smaller study found no difference in incidence of hyponatremia between NS and 0.45% NaCl.[13] In a neonatal study, term newborns with hyperbilirubinemia experienced a higher incidence of hyponatremia when receiving D5W 0.2% NaCl but also a higher incidence of hypernatremia when receiving D5W NS.[14] **Hypotension/shock:** 20 mL/kg of NS over 5–10 minutes that may be repeated. Up to 80 mL/kg may be required during the first hour; however, the child should continuously be assessed for fluid overload.[15,16] In one study, hypertonic (3%) NaCl 15 mL/kg over 30 minutes compared to NS 20 mL/kg (× 1 or 2 boluses) as the initial fluid bolus regimen in pediatric patients with septic shock resulted in less total volume required for resuscitation (23 versus 29 mL/kg) but also a significantly higher increase in serum sodium concentration (10 versus 5 mEq/L).[17] **Dehydration:** 20 mL/kg of NS over 20 minutes; may be repeated to restore intravascular volume.[6] In severe dehydration, multiple boluses that are infused rapidly may be required to prevent shock.[6] After intravascular volume is restored, correction of the fluid deficit should begin along with providing maintenance fluids. **Symptomatic hyponatremia:** The initial goal of sodium replacement is symptom resolution and not correction of the serum sodium to normal. As an estimate, 1 mL/kg of 3% NaCl will raise the serum sodium by 1 mEq/L.[6] More aggressive replacement may be required in patients with severe symptoms such as seizures.[6] Following resolution of symptoms, the infusion should be adjusted to increase serum sodium concentration by no more than 10–12 mEq/L per day.[5,6] Frequent monitoring of serum sodium concentrations is essential. (See Comments section.)

Dosage *(cont.)*	**Severe traumatic brain injury:** 3% saline as bolus doses ranging from 6.5–10 mL/kg (over a 2-hour study period) or as a continuous infusion 0.1–1 mL/kg/hr titrated to maintain intracranial pressure of <20 mm Hg.[18–21] Alternatively, 1.5% saline (268 mEq/L) infused to obtain a desired serum sodium concentration of 145–150 mEq/L has been studied.[22]
Dosage adjustment in organ dysfunction	None required.
Maximum dosage	Maximum dose for NS has not been established. Manufacturer recommends a maximum infusion rate for 3% or 5% saline of 100 mL/hr or 400 mL/day.[23]
Additives	Some products (bacteriostatic sodium chloride) contain benzyl alcohol as a preservative.[24] (See Appendix C for information about potential benzyl alcohol toxicity.)
IV push	NS 20 mL/kg given rapidly may be indicated in severe hypotension/shock.[5,6]
Intermittent infusion	NS 20 mL/kg over 20 minutes to 1 hour in moderate dehydration.[5,6]
Continuous infusion	Usual method of administration.
Other routes of administration	IO.[16]
Maximum concentration	NS via a peripheral line (Osmolarity ~308 mOsm/L). More concentrated saline infusions (i.e., 3% saline [1030 mOsm/L], or 5% saline [1710 mOsm/L]) require infusion via a large peripheral vein.[23] Central venous access is preferred for administration of any hypertonic saline solutions (>0.9%).[24]
Comments	**Significant adverse effects:** Those who slowly develop hyponatremia may be relatively asymptomatic; however, those with a more rapid rate of decline of the sodium concentration may be symptomatic with mild hyponatremia. Symptoms associated with hyponatremia are primarily related to CNS effects and include symptoms of nausea, headache, lethargy, confusion, muscle aches, agitation, and seizures.Too rapid correction of serum sodium (either hyper- or hyponatremia) can result in cerebral edema with symptoms of seizures and coma.[5,6] Too rapid decrease in serum sodium can be treated with 3% saline to acutely increase the serum sodium and reverse the cerebral edema.[5,6]

Sodium Nitroprusside

Brand names	Nitropress, Nipride (Canada)
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that nitroprusside has been confused with norepinephrine and nitroglycerin and patient harm did not occur. Patient harm resulted when nitroprusside was confused with Neo-Synephrine and nicardipine. Nipride has been confused with nesiritide and patient harm did not occur.[2]
Contraindications and warnings	**U.S. boxed warning:** The product must be diluted in D5W prior to infusion.[3] Precipitous decreases in blood pressure (BP) can occur. Patients must be continuously monitored with appropriate equipment and by trained personnel during infusion.[3] Cyanide ions can reach toxic levels during infusion. Failure to attain the desired response after maximum infusion rate (10 mcg/kg/min) for 10 minutes should result in termination of the infusion.[3] **Contraindications:** Treatment of compensatory hypertension due to aortic coarctation or arteriovenous shunting; patients with known inadequate cerebral circulation or in moribund patients undergoing emergency surgery; patients with Leber congenital optic atrophy or with tobacco amblyopia; or patients with acute coronary heart failure with reduced peripheral vascular resistance (e.g., high-output heart failure).[3] **Warnings:** Excessive hypotension and cyanide toxicity are significant risks of nitroprusside administration.[3]
Infusion-related cautions	Too rapid decrease in BP can result in serious and permanent neurological sequelae.[3–6] Blood pressure should be monitored continuously with an arterial line.[3,6,7] It has been recommended that the BP be gradually decreased ≤25% in the first 8 hours after presentation followed by gradual normalization of the BP over 26–48 hours.[8] Nitroprusside should only be infused using an infusion pump (e.g., not via gravity).[3] Use with caution in patients with increased intracranial pressure and those with compensatory hypertension (e.g., infants with arteriovenous shunt or coarctation of the aorta).[3]
Dosage	**Neonates:** 0.25–0.5 mcg/kg/min titrated q 20 min. Usual maintenance dose is less than 2 mcg/kg/min; maximum dose for hypertensive crisis is 10 mcg/kg/min, but for no more than 10 minutes, after which infusion rate should be reduced.[9] In 58 neonates with various disease states (respiratory distress syndrome, persistent pulmonary hypertension of the newborn, shock, systemic hypertension, and pulmonary hypoplasia), infusion rates of 0.2–6 mcg/kg/min for 10 minutes to 126 hours were reported.[10] One neonate (28 weeks gestational age) with respiratory distress syndrome received 2 mcg/kg/min for 24 hours, after which the infusion was weaned off over the next 48 hours. The baby required 45 mL/kg blood transfusion to maintain acceptable systolic blood pressure during the infusion.[11] **Infants and children:** 0.3–0.5 mcg/kg/min initially titrated by 0.25 mcg/kg/min q 5–10 min until desired response is attained, up to a maximum of 10 mcg/kg/min.[3,5,7,8,12–21] Usual maintenance dose requirement is ≤3 mcg/kg/min in children and *adults*. The maximum rate of 10 mcg/kg/min should be infused no longer than 10 minutes.[3]
Dosage adjustment in organ dysfunction	Use cautiously in severe hepatic[3] or renal[22] disease due to an increased risk for thiocyanate toxicity.[3] To minimize the risk of thiocyanate toxicity, a prolonged infusion should not exceed 3 mcg/kg/min; in anuric patients, a prolonged infusion should not exceed 1 mcg/kg/min.[3]

Sodium Nitroprusside

Maximum dosage	10 mcg/kg/min.[3] Cumulative infusions of 500 mcg/kg at rates faster than 2 mcg/kg/min produce cyanide ion more rapidly than the body can eliminate it.[3] In *adults*, 400 mcg/kg/min was infused for short periods.[23]
Additives	Contains 0.335 mEq sodium per 50 mg of sodium nitroprusside.[24,25]
Suitable diluents	The manufacturer recommends D5W only[3]; however, nitroprusside has also been shown to be stable in LR and NS.[24]
Maximum concentration	200 mcg/mL.[3,26] 70 mcg/mL was used in children 8–17 years old.[15] In fluid-restricted patients, 1000 mcg/mL has been used.[27] In *adults*, a concentration of 800 mcg/mL was reported.[28]
Preparation and delivery	**Preparation:** Must be further diluted prior to infusion.[3] (See Suitable Diluents section.) Product may be faint brownish in color; however, it should not be used if blue, green, or red, or with visible particulates.[3] **Photosensitivity:** Protect from light with aluminum foil or other opaque material.[3] Amber plastic coverings may be insufficient protection.[24] It is not necessary to cover the drip chamber or IV tubing.[3] **Compatibility:** For PN compatibility information, please see Appendix D.
IV push	Not indicated.
Intermittent infusion	Not indicated.
Continuous infusion	50–200 mcg/mL.[3,24]
Other routes of administration	IO.[29]
Comments	**Adverse effects:** Excessive hypotension and cyanide toxicity.[3] Cyanide toxicity usually occurs with prolonged use[3]; however, it has been reported after as short a time as a few hours.[30] Those with decreased renal function may be at increased risk.[3,4] One study in children did not find an association between cumulative dose or duration of therapy and increased cyanide levels.[31] Cyanide toxicity results in venous hyperoxemia, lactic acidosis, air hunger, confusion, and death. Acidosis may not occur until more than 1 hour after cyanide concentrations are toxic.[3] During nitroprusside infusions (cumulative dose >10 mg/kg), hemoglobin (Hb) can be sequestered as methemoglobin. Methemoglobinemia (>10% of Hb) results in signs of impaired oxygen delivery despite adequate cardiac output and arterial PaO_2. Methylene blue is an antidote (1–2 mg/kg IV over several minutes) but should be used cautiously.[3] In two pediatric studies including 52 and 63 children, the appearance of adverse events was not a reliable predictor of cyanide toxicity.[21,31] One group determined that the mean dose (2 mcg/kg/min for more than 24 hours)[21] was most predictive of increased cyanide concentrations.[20]

Sodium Nitroprusside

Comments *(cont.)*

Thiocyanate is a product of cyanide metabolism and a route for cyanide elimination. Sodium thiosulfate has been administered with sodium nitroprusside at infusion rates of 5–10 times that of nitroprusside to accelerate the metabolism of cyanide to thiocyanate; however, further study is needed before this can be recommended.[3]

Less commonly, methemoglobinemia and thiocyanate toxicity.[3]

Treatment of cyanide toxicity: Discontinue sodium nitroprusside and administer sodium nitrite and sodium thiosulfate (e.g., commercially available cyanide antidote kit).[3]

Monitoring: Acid–base balance and venous oxygen concentration may suggest cyanide toxicity. Blood pressure should be continuously monitored, preferably intra-arterially.[3] Cyanide and thiocyanate serum concentrations may be warranted in patients receiving extended therapy, doses >2 mcg/kg/min, or with renal[29] or hepatic dysfunction.[3]

Succinylcholine Chloride

Brand names	Anectine, Quelicin
Medication error potential	ISMP high-alert medication (neuromuscular blocking agent) that has an increased risk of causing significant patient harm if it is used in error.[1]
Contraindications and warnings	**U.S. boxed warning:** Use of succinylcholine in children should be reserved for emergency intubation or instances where the airway must be immediately secured (e.g. laryngospasm, difficult airway, full stomach, or for IM use when a suitable vein is inaccessible).[2] Acute rhabdomyolysis with hyperkalemia, ventricular dysrhythmias, cardiac arrest, and death have been reported predominately in healthy appearing children, some of whom had undiagnosed myopathies, but have also occurred in other age groups.[2] (See Rare Adverse Effects/Rhabdomyolysis in the Comments section.) **Contraindications:** Should not be given to individuals with a personal or familial history of malignant hyperthermia, skeletal muscle myopathies, and known hypersensitivity to the drug. Because of severe hyperkalemia and possible cardiac arrest, should not be used in patients after the acute phase of injury following major burns, multiple trauma, extensive denervation of skeletal muscle, or upper motor neuron injury.[2] (See Rare Adverse Effects/Hyperkalemia in the Comments section.) **Other warnings:** Should be used only by those skilled in the management of artificial respiration and only when facilities are instantly available for tracheal intubation and ventilation, including the administration of oxygen under positive pressure and the elimination of carbon dioxide. Should be administered with extreme caution to patients suffering from electrolyte abnormalities and those who may have massive digitalis toxicity, because of the likelihood of serious cardiac arrhythmias or cardiac arrest due to hyperkalemia. (See Rare Adverse Effects/Hyperkalemia in the Comments section.)[2] Should not be administered before unconsciousness has been induced.[2] Succinylcholine is metabolized by plasma cholinesterase and should be used with caution, if at all, in patients known to be or suspected of being homozygous for the atypical plasma cholinesterase gene.[2] (See Other in the Comments section.)
Infusion-related cautions	Rapid administration may cause bradyarrhythmias secondary to vagal stimulation.[2–5] Pretreatment with atropine may reduce this risk.[2,3] (See Dosage section.) Safety precautions must be maintained until full muscle tone has returned.[2]
Dosage	Bradycardia, which may progress to asystole, occurs more often following a second dose of succinylcholine.[2] Its incidence and severity is higher in children than *adults.*[2] Pretreatment with atropine (0.02 mg/kg; minimum 0.1 mg, maximum 0.5 mg)[6] has been recommended for all patients <5 years and for older children and adolescents receiving a second dose of succinylcholine.[7] **Dosing adjustment for obesity:** Dosing for rapid sequence intubation should be based on actual body weight.[8,9] **Test dose:** To evaluate sensitivity to succinylcholine, 0.1 mg/kg (5–10 mg in *adults*) or a slow infusion of a 1-mg/mL solution may be administered cautiously.[2,10] (See Other in the Comments section.) **Induction and maintenance of neuromuscular blockade** **Neonates, nonemergent intubation:** 1–2 mg/kg.[11,12] (AAP recommends that vagolytic and muscle relaxant agents should be considered, and that analgesic agents or anesthetic doses of a hypnotic agent should be administered. Rocuronium or vecuronium is preferred over other available neuromuscular blocking agents.)[11] **Neonates and infants <6 months old:** 1–3 mg/kg[2–4,13–15]

Dosage *(cont.)*	**Infants 6 months to children <2 years old:** 1–2 mg/kg.[2,4,13–15] One reference recommends 3 mg/kg for infants up to 1 year of age, and 2 mg/kg for children 1–2 years old.[3] **Children ≥2 years old and adolescents:** 1 mg/kg.[2,15,16] Doses up to 2 mg/kg may be required.[3,4] Typical *adult* intermittent dosing consists of an initial dose of 0.3–1 mg/kg followed by 0.04–0.07 mg/kg q 5–10 min PRN.[2] Monitoring neuromuscular transmission with a peripheral nerve stimulator is recommended with repeated dosing.[17]
Dosage adjustment in organ dysfunction	No adjustment in renal failure,[18] but use cautiously as succinylcholine can cause hyperkalemia.[2,18] Plasma cholinesterase activity may be decreased in severe renal or hepatic disease.[2]
Maximum dosage	Not to exceed 150 mg when given IM.[2]
Additives	Preserved with methylparaben and/or propylparaben.[2]
Suitable diluents	D5W, D10W, LR, NS, ½NS, D5LR, D5NS, D5¼NS, D5½NS.[19]
Maximum concentration	100 mg/mL for IV push and 2 mg/mL for continuous infusion.[2,20]
Preparation and delivery	**Stability:** Unopened vials are stable 14 days at room temperature. Studies reporting longer stability are manufacturer-specific. Consult a detailed reference or manufacturer product labeling for the most current recommendations.[2,19] Should not be mixed or administered with alkaline solutions.[2]
IV push	20 mg/mL or 100 mg/mL (both available commercially) given over 10–30 seconds.[2,10]
Intermittent infusion	Not administered by this method.
Continuous infusion	Not recommended in infants and children.[2,10] It has been used successfully for neuromuscular relaxation in infants; however, tachyphylaxis and phase II block have occurred during continuous infusion.[21] The risk of malignant hyperthermia also precludes the use of continuous infusions in infants and children.[10]
Other routes of administration	**Deep IM injection** **Neonates:** 2 mg/kg IM.[11] **Infants 1–6 months old:** 5 mg/kg IM.[15] **All other ages:** 3–4 mg/kg, not to exceed a total dose of 150 mg.[2]
Comments	**Rare adverse effects:** Numerous cases of sudden death have been attributed to succinylcholine. These generally are attributed to acute rhabdomyolysis with hyperkalemia and ventricular dysrhythmias; hyperkalemia; malignant hyperthermia; or a combination of all three. If a healthy patient develops unexplained sudden cardiac arrest soon after administration of succinylcholine, immediate treatment for hyperkalemia should be instituted.[2] One study reported the successful use of extracorporeal membrane oxygenation.[22] If indicated, treatment of malignant hyperthermia should also be instituted (see below).[2]

Succinylcholine Chloride

Comments *(cont.)*

Rhabdomyolysis: Succinylcholine has been reported to cause acute rhabdomyolysis and death in healthy children.[2,23,24] Many of these children were subsequently reported to have Duchenne muscular dystrophy.[2] Rhabdomyolysis may present with peaked T-waves and sudden cardiac arrest within minutes of administration. It appears to be most common in males ≤8 years old but has also been reported in adolescents.[2] Routine resuscitative measures are generally unsuccessful. However, extraordinary and prolonged resuscitative efforts have resulted in successful management in some cases.[2]

Hyperkalemia: Hyperkalemia may occur, especially in patients who have trauma, severe burns, or neuromuscular disease, which may result in an increase in acetylcholine receptors.[2,25] The risk is dependent on the extent and location of the injury.[2,26,27] The precise time of onset and the duration of the risk period are not known but increases over time and usually peaks at 7–10 days after the injury.[2] Patients with preexisting hyperkalemia should not receive succinylcholine.[2] Hyperkalemia occurs almost immediately after succinylcholine, peaks in 5 minutes, and lasts less than 10–15 minutes.[25] Treat with calcium, bicarbonate, glucose with insulin, and hyperventilation.[25] Should be used cautiously in patients with chronic abdominal infection, subarachnoid hemorrhage, or conditions causing degeneration of central and peripheral nervous systems.[25]

Malignant hyperthermia: The risk of developing succinylcholine-associated acute malignant hyperthermia increases with the concomitant administration of volatile anesthetics.[2] It frequently presents as intractable spasm of the jaw muscles (masseter spasm), which may progress to generalized rigidity, increased oxygen demand, tachycardia, tachypnea, and profound hyperpyrexia.[2,27] Skin mottling, rising temperature, and coagulopathies may occur later.[2] If sign or symptoms are present, succinylcholine should be discontinued, and correction of acidosis, support of circulation, assurance of adequate urinary output, and institution of measures to control rising temperature should be instituted. IV dantrolene sodium is recommended as an adjunctive therapy.[27]

Drug interactions: Aminoglycosides can cause neuromuscular blockade and potentiate the effects of neuromuscular blockers.[28] Because succinylcholine is associated with numerous drug interactions, consult appropriate resources for dosing recommendations before combining any drug with succinylcholine.

Pharmacodynamic considerations: Infants and children are more resistant than *adults* to the neuromuscular blockade produced by succinylcholine.[2–4]

Other: Plasma cholinesterase activity may be decreased or absent in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for an atypical plasma cholinesterase gene), pregnancy, severe liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema.[2] It may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors, and by irreversible inhibitors of plasma cholinesterase (e.g., organophosphate insecticides, echothiophate, and certain antineoplastic drugs).[2] Patients homozygous for atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of succinylcholine; this has been described in a neonate, who had prolonged apnea (3 hr) after a single dose of succinylcholine.[2,29] In these patients, a test dose may be administered to evaluate sensitivity to succinylcholine.[2] Apnea or prolonged muscle paralysis should be treated with controlled respiration.

SUFentanil Citrate

Brand names	Sufenta
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP reports that SUFentanil has been confused with fentaNYL.[2] USP also reports that SUFentanil has been confused with alfentanil; no patient harm resulted.[3] USP reports that SUFentanil citrate has been confused with fentaNYL citrate; patient harm resulted.[3] Sufenta may be confused with Sudafed or Survanta.[4]
Contraindications and warnings	**Contraindications:** SUFentanil is contraindicated in patients with a hypersensitivity to the drug or know intolerance to opioid agonists.[5] **Warnings:** SUFentanil should be administered only by persons specifically trained in the use of IV and epidural anesthetics and management of the respiratory effects of potent opioids. An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.[5]
Infusion-related cautions	Significant bradycardia, muscle or chest wall rigidity (dose-related),[6] and apnea may occur early in administration of SUFentanil or following rapid administration. Pretreatment with atropine and a nondepolarizing neuromuscular blocking agent may aid in minimizing these adverse effects.[5] Naloxone reverses respiratory depression induced by SUFentanil; the respiratory depression induced by SUFentanil may last longer than the duration of naloxone, necessitating additional naloxone doses.[5]
Dosage	Dosages vary depending on the desired degree of analgesia/anesthesia and adjunctive therapies (e.g., halothane, propofol). Repeat doses should be increased or decreased based on response to initial dose.[5] **Dosing adjustment for obesity:** Use lean body weight when dosing patients whose weight is >20% of their ideal body weight.[5,7] (See Appendix B.) **Infants and children (<2 years)** **Anesthesia:** Dose of 5–20 mcg/kg (0.5 mcg/kg when combined with halothane and nitric oxide)[6,8,9] followed by a continuous infusion of 1–2 mcg/kg/hr.[8] **Analgesia (mechanically ventilated patients):** Ten neonates with respiratory distress syndrome received 0.28–0.42 mcg/kg over 15 min as incremental doses along with a continuous infusion starting at 0.14 mcg/kg/hr (median dose required was 0.4 mcg/kg/hr; median duration 26 hours). The infusion was titrated in increments of 0.07–0.14 mcg/kg/hr.[10] Thirty neonates who underwent cardiac surgery received a postoperative infusion of 2–4 mcg/kg/hr for 24 hours.[8] Fifteen preterm neonates (26–34 weeks gestational age) with respiratory distress received 0.5 mcg/kg over 10 minutes followed by an infusion of 0.2 mcg/kg/hr.[11] **Children (2–12 years)** **Anesthesia:** Initial 10–25 mcg/kg[5,12]; maintenance doses up to 25–50 mcg PRN.[5] **Children ≥12 years and *adults*[5]** **Adjunct to anesthesia during brief operative cases (1–2 hours):** Initial 1–2 mcg/kg as intermittent dose or continuous infusion; maintenance 10–25 mcg PRN. Total dose not to exceed an average of 1 mcg/kg per hour of the operation.

Dosage *(cont.)*	**Adjunct to anesthesia during operative cases lasting 2–8 hours:** Initial 2–8 mcg/kg as intermittent dose or continuous infusion; maintenance 10–50 mcg PRN. Total dose not to exceed an average of 1 mcg/kg per hour of the operation. **Anesthesia (high dose):** Initial 8–30 mcg/kg as an intermittent dose or continuous infusion; maintenance 0.5–10 mcg/kg PRN. Not to exceed a total of 30 mcg/kg.
Dosage adjustment in organ dysfunction	No dosage adjustment required in patients with renal dysfunction.[13] The manufacturer recommends caution when administering SUFentanil to patients with hepatic or renal impairment.[5]
Maximum dosage	Doses should be titrated to an appropriate level of anesthesia or pain control with manageable adverse effects.[5] In *adults* a maximum dose of 30 mcg/kg has been recommended for anesthesia and 8 mcg/kg for analgesia.[5] For procedures lasting >1 hour, the total SUFentanil dose should not exceed 30 mcg/kg.[5] For all procedures, the total infusion dose should not exceed 1 mcg/kg/hr of anticipated procedure time.[5]
Additives	None.
Suitable diluents	D5W, NS.[14]
Maximum concentration	50 mcg/mL.[5]
Preparation and delivery	See the Other Routes of Administration section for comments on intranasal delivery.
IV push	1–50 mcg/mL given over 2–5 minutes.[5,6,9,12]
Intermittent infusion	1–50 mcg/mL.[5,14]
Continuous infusion	1–50 mcg/mL.[5,14]
Other routes of administration	Although SUFentanil has been given by IM administration,[14] it is generally not administered via this route. It can be given by epidural injection.[5,14] Intranasal SUFentanil has been described. Three studies (n = 160 total; 0.5–10 years of age) reported using 1.5–3 mcg/kg as premedication for surgery.[15–17] Three additional studies (n = 60 total; 1–10 years of age) reported combination SUFentanil and midazolam, both given intranasally, for dental procedures or laceration repair. Doses of SUFentanil ranged from 0.75–1.33 mcg/kg (two studies limited the dose to 20 mcg) and midazolam doses ranged from 0.2–0.3 mg/kg (max 6 mg in one study).[18–20] Authors reported nasal administration techniques as either delivery via a needleless syringe[16–18] or as a nasal spray[20] using a concentration of 50 mcg/mL.[16, 20]
Comments	**Significant adverse effects:** Caution should be used when administering SUFentanil to patients with head trauma. It has been associated with increases in intracranial pressure in this population.[21] **Pharmacokinetic considerations:** The elimination half-life is shorter in infants and children and longer in neonates compared to that of adolescents and *adults*.[5,22] Clearance can be further reduced by up to one-third in neonates with cardiovascular disease.[5]

SUFentanil Citrate

Comments *(cont.)* Ten male children with glucose-6-phosphate dehydrogenase deficiency safely received SUFentanil 0.2 mcg/kg for perioperative analgesia without evidence of hemolysis.[23]

Other: SUFentanil produced EEG changes in preterm neonates resembling sleep states and burst suppression.[11]

Tacrolimus

Brand names	Prograf
Medication error potential	Look-alike, sound-alike drug names. USP reports that tacrolimus has been confused with pimecrolimus, sirolimus, tamsulosin, and tolterodine.[1] ISMP reports confusion of Prograf with Prozac.[2]
Contraindications and warnings	**U.S. boxed warning:** Patients undergoing immunosuppressive therapies are at increased risk for infection and the development of lymphoma. Tacrolimus should only be prescribed by physicians with experience in immunosuppressive therapies. Patients receiving tacrolimus should be treated in facilities staffed and equipped with adequate laboratory and supportive medical resources. See the product literature for more complete information.[3] **Contraindications:** Patients with hypersensitivity to tacrolimus or who are allergic to polyoxyl 60 hydrogenated castor oil.[3]
Infusion-related cautions	Anaphylaxis to the polyoxyl 60 hydrogenated castor oil vehicle has occurred.[3] Observe patient continuously for ≥30 minutes after start of infusion and frequently thereafter. Oxygen and an aqueous solution of epinephrine should be at the bedside during the infusion.[3]
Dosage	Tacrolimus should be started no earlier than 6 hours after transplantation. Patients should be changed to oral therapy as soon as possible. When converting from IV to oral dosing, the first oral dose should be given 8–12 hours after the infusion is stopped.[3] **Heart, liver, or kidney transplantation:** 0.03–0.05 mg/kg/day by continuous infusion.[3] For kidney transplants, the dose should be administered between 6 and 24 hours after transplant but should be delayed until renal function has recovered (SCr <4 mg/dL).[3] Use lowest dose that attains the desired blood (preferred), serum, or plasma concentration.[3] In children after heart transplant doses of 0.03–0.05 mg/kg/day as a continuous infusion were used if urine output was >1 mL/kg/hr. These investigators recommended initial monitoring of blood concentrations 12 hours after the beginning of the infusion.[4] Following liver transplant, doses have ranged from 0.03–0.15 mg/kg/day by continuous infusion.[3,5–10] One large, multicenter study in *adults* and children initially infused 0.075 mg/kg over 4 hours q 12 hr, but the dose was decreased to 0.05 mg/kg after an increase in renal toxicity was noted.[10] In general, children require larger doses following liver transplant than *adults*.[3] In a pharmacokinetic study, children who received an intact child's liver had a greater than expected clearance of tacrolimus, while those who received a cut-down liver from an *adult* had lower clearance than expected.[11] **Graft-versus-host disease (GVHD) after bone marrow transplantation:** 0.02 mg/kg/day as a continuous infusion beginning the day before transplantation and mycophenolate mofetil or methotrexate administered concomitantly has been used.[12–14] Another group treated an 18-year-old and a 9-year-old with steroid-resistant, severe, acute GVHD with 0.1 mg/kg/day as a continuous infusion, maintaining blood concentrations of 25–35 ng/mL.[15] (See Comments section.)
Dosage adjustment in organ dysfunction	**Renal and hepatic insufficiency (Pugh ≤10):** Initial doses should be the lowest in the recommended range and trough concentrations should be closely monitored.[3,16]
Maximum dosage	Not established. 0.44 mg/kg/day has been given to *adults*.[10]
Additives	Contains polyoxyl 60 hydrogenated castor oil (HCO-60) and dehydrated alcohol.[3,17]

Tacrolimus

Suitable diluents	D5W, NS.[3,17]
Maximum concentration	0.02 mg/mL.[3,17]
Preparation and delivery	**Stability:** Tacrolimus absorbs to PVC; therefore, store in polyolefin containers or glass IV bottles. Infusion through PVC anesthesia extension tubing, PVC IV administration set tubing, or fat emulsion tubing does not result in decreased blood concentrations.[17–19] Surfactants in injectable products have been associated with leeching of the plasticizer di-2-ethylhexyl phthalate (DEHP) when stored or administered in PVC containers. Only glass, polyethylene or non-DEHP plasticized administration sets should be used for tacrolimus infusions.[17] **Compatibility:** See Appendix D for PN compatibility information.
IV push	Not indicated.
Intermittent infusion	Has been infused over 4 hours.[10]
Continuous infusion	Usually infused over 24 hours.[3–7,12,13,15]
Other routes of administration	Not indicated.
Comments	**Adverse effects:** The risk of lymphoproliferative disorders is greater in young children who are at risk for Epstein-Barr virus infection.[3] Reversible left ventricular wall thickening was noted in pediatric and *adult* patients who had trough concentrations >15 ng/mL.[3,20] Hypertension occurs frequently. Serum potassium should be monitored to be sure hyperkalemia has not developed.[3] **Pharmacokinetics:** To minimize toxicity, monitor whole blood, serum, or plasma concentrations.[3,6] Use the same matrix and assay type consistently for a given patient.[3] Whole blood is the preferred matrix and samples should be collected in EDTA tubes.[3] Trough concentrations should range from 5–20 ng/mL for whole blood.[3] Accuracy of whole blood measurements is diminished when microparticle enzyme immunoassay methods are used and concentrations are <9 ng/mL. Liquid chromatography—tandem mass spectrometry assays are associated with greater sensitivity and precision.[21] **Drug interactions:** Tacrolimus is a substrate of CYP3A4 and can be inhibited or induced by other drugs.[3] Consult appropriate resources for dosing recommendations before combining any drug with tacrolimus.

Temsirolimus

Brand names	Torisel
Medication error potential	None.
Contraindications and warnings	**Contraindications:** Patients with bilirubin >1.5 × ULN (upper limit of the normal range) should not receive temsirolimus.[1] **Other warnings:** Hypersensitivity, including anaphylaxis, can occur early in the first infusion of temsirolimus. Patients should be closely monitored throughout the duration of the infusion. Appropriate medical care should be available in the event of anaphylaxis. Discontinuation of the infusion and administration of antihistamine should be used to treat hypersensitivity reactions. Once resolved the infusion may be restarted at a slower rate.[1] Administer an H_1 antagonist and/or an IV H_2 antagonist 30 minutes prior to resuming infusion.[1] Use with caution in patients with mild hepatic impairment. Dose reduction may be necessary.[1] Use with caution in the perioperative period, as abnormal wound healing may occur.[1]
Infusion-related cautions	See Contraindications and Warnings section.
Dosage	**Premedication with IV diphenhydramine, 30 minutes prior to each dose is recommended.[1] Dosage should be held for absolute neutrophil counts <1000/mm³, platelet count <75,000/mm³, or CTCAE (common terminology criteria for adverse events) grade 3 or greater adverse reactions.[1]** **Recurrent/refractory solid tumors:** 75 mg/m² IV once weekly.[2] In a phase II trial in children 1–21 years of age with neuroblastoma, rhabdomyosarcoma or high-grade glioma, one complete response was seen in a neuroblastoma patient. Stable disease was noted in 7 of 17 patients with high-grade glioma and 6 of 19 patients with neuroblastoma. A partial response at week 18 was seen in 1 of 16 patients with rhabdomyosarcoma.[2] **Advanced or metastatic Ewing sarcoma:** 25–37.5 mg IV once weekly with cixutumumab 6 mg/kg IV weekly.[3] Twenty patients with Ewing sarcoma or desmoplastic, small round cell tumor, ages 14–41 were administered combination therapy on 4-week cycles. Complete response was seen in 1 of 17 Ewing sarcoma patients with tumor regression in 5 of 17.[3] **Advanced renal cell carcinoma (*adults*):** 25 mg IV once weekly.[1]
Dosage adjustment in organ dysfunction	In *adults*, mild hepatic impairment, defined as bilirubin >1–1.5 × ULN or AST (aspartate aminotransferase) >ULN with bilirubin ≤ULN: 15 mg once weekly.[1] Moderate-to-severe hepatic impairment, defined as bilirubin >1.5 × ULN: contraindicated.[1]
Maximum dosage	220 mg/m².[1]
Additives	Polysorbate 80, propylene glycol, dehydrated alcohol.[1]
Suitable diluents	NS. Do not mix with other solutions or medications.[1]
Maximum concentration	10 mg/mL.[1]

Temsirolimus

Preparation and delivery	Protect from excessive room light and sunlight during preparation. Use two-step process for preparation: (1) dilute vial of temsirolimus with 1.8 mL of supplied diluent to produce 30 mg/3 mL (mix well and allow air bubbles to subside); (2) withdraw the required amount of concentrate-diluent mixture as prepared in step 1 and further dilute into a 250-mL bag of NS (mix by inversion and avoid excessive shaking; protect from excessive room light and sunlight; administer within 6 hours).[1] Administration materials should be glass, polyolefin, or polyethylene to avoid excessive loss of product and diethylhexyl phthalate (DEHP) extraction.[1] When PVC administration has to be used, it should not contain DEHP.[1] Use with an in-line polyethersulfone filter with pore size <5 microns.[1]
IV push	Not recommended.
Intermittent infusion	Infuse over 30–60 minutes weekly.[1]
Continuous infusion	Not recommended.
Other routes of administration	Not recommended.
Comments	**Significant adverse effects:** Hyperglycemia, immunosuppression, interstitial lung disease, hyperlipidemia, bowel perforation, renal failure, wound healing complications, intracerebral hemorrhage have been reported.[1] Patients should be closely monitored. The most common adverse reactions ($\geq$30%) are rash, asthenia, mucositis, nausea, edema, and anorexia.[1] The most common laboratory abnormalities ($\geq$30%) are anemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, lymphopenia, elevated alkaline phosphatase, elevated SCr, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia.[1] **Significant drug interactions:** Strong inducers of CYP3A4/5, such as dexamethasone, carbamazepine, phenytoin, phenobarbital, rifampin, and rifampicin, may decrease exposure of the active metabolite (sirolimus). A dose adjustment should be considered.[1,4] Concomitant use of St. John's Wort should be avoided, due to unpredictable temsirolimus concentrations.[1] Strong inhibitors of CYP3A4 such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin may increase concentrations of the active metabolite sirolimus. A dose adjustment should be considered.[1,5] Concomitant use of temsirolimus and sunitinib has resulted in dose-limiting toxicity requiring hospitalization.[1] **Other:** Live virus vaccines (measles, mumps, rubella; varicella; rotavirus) should be avoided during treatment.[1]

Terbutaline Sulfate

Brand names	Brethine, generic
Medication error potential	Look-alike, sound-alike drug names. ISMP reports that Brethine has been confused with Methergine.[1] USP reports that Brethine has been confused with Methergine and thiethylperazine. Terbutaline has been confused with terazosin, terbinafine, and thiethylperazine.[2]
Contraindications and warnings	**Contraindications:** Hypersensitivity to terbutaline, sympathomimetic amines, or any product components.[3]
Infusion-related cautions	The manufacturer does not recommend IV administration.[3]
Dosage	**Severe asthma exacerbations:** 0.01 mg/kg SC q 20 min for 3 doses then q 2–6 hr PRN (in *adults* 0.25 mg q 20 min for 3 doses).[4] However, the *National Asthma Education and Prevention Program Expert Panel Report 3* states that there is no proven advantage of systemic terbutaline therapy over aerosol.[4] **Status asthmaticus:** Five adolescents received 0.25–0.3 mg SC q 12–15 min with a maximum of 10 mg in 24 hours.[5] In 11 children 7–33 months old who failed to respond to nebulizer treatments, a SC infusion of 0.2–0.3 mcg/kg/min was given over 20 minutes followed by 0.1 mcg/kg/min for an average of 6 days.[6] **IV dosing:** An IV loading dose of 2–20 mcg/kg (most studies used 5–10 mcg/kg) over 5–30 minutes followed by 0.08–4 mcg/kg/min (one reference suggests an upper limit of 10 mcg/kg/min)[7] with increases of 0.1–0.4 mcg/kg/min q 30 min to desired response or toxicity.[7–14] Alternatively, an initial IV infusion of 0.05–0.1 mcg/kg/min increased by 0.1–0.2 mcg/kg/min q 2 hr up to 5–10 mcg/kg/min according to respiratory symptoms.[15] Usual maximum infusion rates were ≤5 mcg/kg/min.[9,10,12–14,16] **Chronic asthma:** In eight children 8–14 years old with chronic severe asthma, a continuous SC infusion of 2.5–5 mg/day increased to 10 mg/day as indicated (improvement in symptoms) and tolerated was used for ≥2 months.[17] **Hyperkalemia:** See recommended IV and SC asthma dosing above.[7] **Treatment of inadvertent vasoconstrictor injection:** A series of case reports on a 13-year-old, a 31-year-old, and a 39-year-old who accidentally discharged an EPINEPHrine autoinjector into their thumbs reported that local injection of 1 or 3 mL of SC terbutaline (1 mg in 10 mL NS) was an effective alternative to phentolamine.[18]
Dosage adjustment in organ dysfunction	No dosage adjustment required in renal dysfunction.[19]
Maximum dosage	20 mcg/kg as an IV loading dose.[14] 10 mcg/kg/min IV for 6 hours was reported in an adolescent.[15] 0.4 mg SC.[7]
Additives	Contains sodium chloride and edetate disodium dihydrate.[3]
Suitable diluents	D5W, ½NS, NS.[20]

Terbutaline Sulfate

Maximum concentration	1 mg/mL (undiluted).[3,20] 0.5 mg/mL was used for SC infusion.[17]
Preparation and delivery	**Stability:** Sensitive to light and excessive heat.[20] Product should be stored in a controlled environment and protected from light and freezing.[20]
IV push	Over 5–10 minutes.[7,8,21]
Intermittent infusion	Generally administered as SC doses or infusions, or as IV loading doses over 5–30 minutes with continuous infusions. (See Dosage section.) IV loading doses have been repeated every 30 minutes based on patient response.[9]
Continuous infusion	1 mg/mL has been infused continuously IV.[11] 0.5 mg/mL has been infused continuously SC.[17]
Other routes of administration	SC, IO.[7]
Comments	**Adverse effects:** Increased heart rate,[6,8,15,16] increased systolic and decreased diastolic blood pressure,[8,15] tremor,[8,17] headache,[8] and hypokalemia[16] have been reported. An 11-year-old who received 10 mcg/kg/min for 6 hours had no evidence of arrhythmias, and creatine phosphokinase MB isoenzyme (CPK-MB) was normal.[15] However, in that same study three children receiving a lower terbutaline dose (two were also receiving aminophylline) did have an elevated CPK-MB concentration. Two of 18 children developed ST segment depression following terbutaline and epinephrine. There was no correlation between CPK values and arrhythmias or ST changes. A prospective evaluation of IV terbutaline's effect on cardiac parameters found no clinically significant cardiac toxicity; patients in this study received a mean maximum 2.4 mcg/kg/min for a mean duration of 53 hours.[13] The incidence of tremor and tachycardia may be increased in those receiving theophylline concomitantly.[8] Bruising, tenderness, and site infection have been reported with continuous SC infusion.[17] **Pharmacokinetics:** Although larger doses are used in children than in *adults*, there is no pharmacokinetic basis to support the need for larger doses.[21] **Drug interactions:** Terbutaline may increase theophylline clearance.[22] **Monitoring:** Blood pressure should be monitored frequently. ECG and oxygen saturation should be monitored continuously. Consider monitoring serum potassium due to the potential risk of hypokalemia.[7]

Thiopental Sodium

Brand names

Pentothal

Medication error potential

High-alert medication (anesthetic and moderate sedation) that has an increased risk of causing significant patient harm if it is used in error.[1]

Look-alike, sound-alike drug names. Confusion between thiopental and Nembutal and between Pentothal and Nembutal has been noted and has resulted in patient harm.[2]

Contraindications and warnings

Contraindications: Hypersensitivity to thiopental, barbiturates, or any component of the formulation.[3] Absence of suitable veins for IV administration; should not be administered by intra-arterial injection.[3] Variegate porphyria (South African) or acute intermittent porphyria.[3]

Relative contraindications include severe cardiovascular disease, hypotension, or shock conditions in which the hypnotic effect may be prolonged or potentiated (e.g., excessive premedication, Addison disease, hepatic or renal dysfunction, myxedema, increased BUN, severe anemia, asthma/status asthmaticus, and myasthenia gravis).

Warnings: May be habit forming.[3] Be prepared to provide respiratory support. Monitor oxygen saturation and keep oxygen available.[3]

Infusion-related cautions

Respiratory depression, apnea, laryngospasm, and hypotension may occur if administered too rapidly.[3]

High alkaline pH (10.6) may cause tissue necrosis upon extravasation.[3] (See Appendix E for management of intra-arterial injection.)

Dosage

Anesthesia

Induction: Doses have ranged from 4–8.6 mg/kg over 10–60 minutes.[3–7] Although some have suggested that the induction doses of thiopental should be larger (relative to weight) in children (5–8 mg/kg)[8] and lower in neonates (3–4 mg/kg),[9] others have found no difference in dosing based on age.[10,11] If clinically indicated, 0.1 mg/kg/sec may be given until the face mask is tolerated.[12] Although rapid injection can cause hypotension and decreased cardiac output, 5 mg/kg have been given over 10 seconds when rapid induction was needed.[5]

Maintenance: 1 mg/kg PRN.[3]

Elevated intracranial pressure

Acute increases: 1.5–3.5 mg/kg, repeat PRN.[3,4]

Sustained elevations (medically induced coma)

Neonates: A loading dose of 10–30 mg/kg[13–15] followed by 2–4 mg/kg/hr as a continuous infusion.[13,14] Two studies evaluated the effects of short-term[14,15] and prolonged coma with thiopental on outcome in neonates with asphyxia and reported no improvement; however, a greater complication rate (i.e., hypotension) was noted.[14,15]

Infants and children: A loading dose of 10–30 mg/kg.[13,16–18] Some investigators recommend administration of two loading doses: 20 mg/kg over 1 hour followed by 10 mg/kg over 6 hours.[13] The loading dose should be followed by a continuous infusion of 1–2 mg/kg/hr and should be titrated based on clinical response and/or serum thiopental concentration (20–40 mg/L).[13,16,17]

Procedural sedation (for procedures <15 minutes): Has been given rectally for this purpose[19]; however, other barbiturates are more frequently used. (See Pentobarbital monograph.)

Dosage *(cont.)*	**Status epilepticus** **Loading:** 10–30 mg/kg.[20,21] **Maintenance:** 5–55 mg/kg/hr.[21] Total doses of thiopental used to obtain and maintain burst suppression were 15–50 g over 48–120 hours and correlated with plasma thiopental levels of 25–40 mg/dL.[21] Most clinicians begin at 5 mg/kg/hr and gradually increase by 1–2 mg/kg/hr for 6–8 hours until all electrical brain activity is suppressed.[22,23]
Dosage adjustment in organ dysfunction	Because the hypnotic effect may be prolonged in renal or hepatic disease, use cautiously in these patients.[3,24] Adjust dose in renal dysfunction.[24,25] If CrCl is <10 mL/min, give 75% of normal dose.[22,26] May need to reduce dosage in hepatic failure/cirrhosis, but no specific recommendations.[25]
Maximum dosage	Not established.
Additives	4.9 mEq sodium/g of thiopental sodium.[3,27]
Suitable diluents	D2.5, D5W, NS, ½NS, D2.5NS, D2.5¼NS, D5¼NS, D5½NS, dextran 6% in D5W, and dextran 6% in NS.[3,27] SW should *not* be used for preparing solutions <2% thiopental since the resulting hypotonic solutions will cause hemolysis.[27]
Maximum concentration	50 mg/mL.[3]
Preparation and delivery	**Stability:** 3 days at room temperature (20°C to 25°C) and 7 days when refrigerated (2°C to 8°C).[27]
IV push	Over 20–30 seconds.[26] Twenty infants, age 12 months, received 5 mg/kg over 10 seconds for rapid anesthesia induction[12] and 10 mg was given over 2 minutes to neonates with resistant seizures without adverse effects.[20]
Intermittent infusion	20–50 mg/mL given over 10–60 minutes with rate titrated according to blood pressure.[13,14,26,28]
Continuous infusion	2–4 mg/mL in D5W or NS.[3]
Other routes of administration	IM administration not recommended due to tissue necrosis.[3,27]
Comments	**Rare adverse effects:** Renal failure may occur as a complication of barbiturate treatment. Monitor BUN and SCr.[29] Anticonvulsant hypersensitivity syndrome is an acute, life-threatening, idiosyncratic reaction that has been reported in patients receiving phenytoin, phenobarbital, carbamazepine, primidone, and lamotrigine.[29–31] Symptoms generally develop within 1–12 weeks following initiation and include a classic triad of fever, rash, and lymphadenopathy.[29–31] Peripheral blood leucocytosis and eosinophilia and internal organ involvement may also be noted. Immediate discontinuation of the suspected anticonvulsant is essential for good outcome.[29–31] Cross-reactivity among the aromatic anticonvulsants has been noted; hence, these should not be used as alternative agents.[29–31]

Thiopental Sodium

Comments *(cont.)*

Monitoring: High-dose thiopental leads to a pronounced fall in serum potassium; therefore, monitor serum potassium.[32] Therapeutic serum concentrations are 1–5 mg/L (hypnotic); 100 mg/L (coma); 7–130 mg/L (anesthesia).[26]

Drug interactions: Consult appropriate resources for dosing recommendations before combining any drug with thiopental.

Pharmacokinetic considerations: Recovery time after large or repeated doses may be more rapid for infants and children compared to *adults* because of a higher clearance.[33]

Ticarcillin Disodium–Clavulanate Potassium

Brand names

Timentin

Medication error potential

Look-alike, sound-alike drug names.

USP reports Timentin may be confused with Tygacil and Ticar.[1]

Contraindications and warnings

Contraindications: in patients with a known hypersensitivity to ticarcillin, clavulanate, or any of the penicillins.[2]

Warnings: Serious hypersensitivity and occasionally fatal anaphylactic reactions have been reported.[2] These are more likely in patients who are sensitive to multiple allergens (e.g., asthma) and in those with a history of type I reaction to penicillin or cephalosporins.[2] (See Appendix C for specific information.)

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]

Infusion-related cautions

If a decision is made to give this medication to a patient with known penicillin hypersensitivity, the patient should be closely observed for allergenicity. Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management. Pain on injection and thrombophlebitis have been noted.[2]

Dosage

Dosage is based on ticarcillin component. Although clavulanate is a beta-lactamase inhibitor that extends the spectrum of ticarcillin, it has little antibacterial activity.[2]

In patients with meningeal seeding from a distant infection site or in whom meningitis is suspected or documented, or in patients who require prophylaxis against CNS infection, an alternate agent with demonstrated clinical efficacy in this setting should be used.[2]

Neonates: Safety and efficacy has not been established in those <3 months of age.[2]

PNA	<1200 g	1200–2000 g	≥2000 g
<7 days	150 mg/kg/day divided q 12 hr[3]	150–160 mg/kg/day divided q 12 hr[3–5]	225–240 mg/kg/day divided q 8 hr[3,5]
≥7 days		225 mg/kg/day divided q 8 hr[3]*	300 mg/kg/day divided q 8 hr[3]

*Until 4 weeks of age.

One study of 11 premature neonates weighing <2200 g suggested a dose of 200 mg/kg/day divided q 6 hr.[6]

Infants and children

Mild-to-moderate infections: 100–200 mg/kg/day divided q 6 hr.[3]

Severe infections: 200–300 mg/kg/day divided q 4–6 hr.[2,3,7–12]

Dosage adjustment in organ dysfunction

Adjust dose in renal dysfunction.[2,13] If CrCl is >30 mL/min, give a normal dose; if CrCl is 10–29 mL/min, give 50–75 mg/kg q 8 hr; if <10 mL/min, give 50–75 mg/kg q 12 hr; and if <10 mL/min and hepatic insufficiency, give 50–75 mg/kg q 24 hr.[13] Alternatively, the manufacturer recommends if CrCl 30–60 mL/min, give a two-third normal dose q 4 hr; if CrCl 10–30 mL/min, give a two-third dose q 8 hr; if CrCl <10 mL/min, give a two-third dose q 12 hr; and if CrCl <10 mL/min with hepatic insufficiency, give a two-third dose q 24 hr.[2]

Ticarcillin Disodium–Clavulanate Potassium

Maximum dosage	300 mg/kg/day,[2,3] up to 400 mg/kg/day has been reported as safe in patients with cystic fibrosis.[14] Not to exceed 3 g/dose or 24 g/day, in those >12 years of age.[2,3]
Additives	Contains ~4.51 mEq of sodium and 0.15 mEq of potassium per g of ticarcillin.[2,15] The frozen injection of 3.1 g/100 mL contains 0.187 mEq/mL of sodium and 0.005 mEq/mL of potassium.[2,15]
Suitable diluents	D5W, LR, SW, or NS.[15]
Maximum concentration	<100 mg/mL (ticarcillin).[15] 43 mg/mL in NS, 48 mg/mL in D5W, and 86 mg/mL in SW.[15]
Preparation and delivery	**Delivery system issues:** The mixing of ticarcillin with an aminoglycoside in vitro can result in substantial inactivation of the aminoglycoside. (See Appendix C for more specific information.) **Stability:** Store intact vials at <24°C.[15] Solutions in NS or LR are stable for 24 hours at room temperature, 7 days when refrigerated, or 30 days when frozen. Solution in D5W is stable for 24 hours at room temperature, 3 days when refrigerated, or 7 days when frozen. After freezing, thawed solution is stable for 8 hours at room temperature. For a premixed solution, store frozen at ≤−20°C. Thawed solution is stable for 24 hours at room temperature or 7 days under refrigeration. Do not refreeze. Darkened solution indicates loss of potency of clavulanate.[2,15] **Compatibility:** See Appendix D for PN compatibility information.[16]
IV push	Not used.
Intermittent infusion	Over 30 minutes.[2,15]
Continuous infusion	Not used. One report in *adults*.[17]
Other routes of administration	None.
Comments	**Rare adverse effects:** Neurotoxic (e.g., lethargy, confusion, twitching, multifocal myoclonus, localized or generalized epileptiform seizures) may occur with large doses of penicillins, especially in patients with renal insufficiency.[2,18–20] Thrombocytopenia and bleeding disorders associated with abnormalities in clotting time, platelet aggregation, and prothrombin time have been reported.[2,21] These are more likely to occur in patients with renal impairment.[2] If bleeding manifestations appear, treatment should be discontinued and appropriate therapy instituted. Elevation of serum transaminases, serum alkaline phosphatase, serum lactate dehydrogenase, and serum bilirubin have been noted.[2] Hepatitis and cholestatic jaundice have also been reported.[2,22] **Laboratory interference:** High urine concentrations may produce false–positive protein reactions (pseudoproteinuria) when testing is performed by sulfosalicylic acid and boiling test, acetic acid test, biuret reaction, and nitric acid test. The bromphenol blue reagent strip test (MULTI-STIX) appears reliable.[2] The presence of clavulanic acid may cause a nonspecific binding of IgG and albumin by red cell membranes leading to a false–positive Coombs test.[2]

Tigecycline

Brand names	Tygacil
Medication error potential	USP reports confusion of Tygacil with Ticar and Timentin.[1]
Contraindications and warnings	**Contraindications:** In those with known hypersensitivity to tigecycline.[2] **Warnings:** Tigecycline is a tetracycline derivative and should be administered cautiously in patients with hypersensitivity to tetracycline.[2] Life-threatening anaphylaxis/anaphylactoid reactions have occurred. Use of tetracyclines during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent tooth discoloration (yellow-gray-brown).[2,3] This is more common during long-term use but has been observed following repeated short-term courses.[3] Tetracycline drugs should not be used in this age group. Elevation in transaminases, total bilirubin concentration, and prothrombin time have been noted and isolated cases of significant hepatic dysfunction/failure have occurred.[2] Patients who develop abnormal liver function tests should be monitored for worsening function and the risk to benefit of continuing therapy should be assessed.[2] Lower cure rates and higher mortality were seen when patients with ventilator-associated pneumonia were treated with tigecycline.[2] Use caution when giving as monotherapy in those with complicated intra-abdominal infection secondary to clinically apparent intestinal perforation as sepsis/septic shock has been reported.[2] Although APACHE II scores were different from baseline, the relationship of this outcome to treatment cannot be established.[2] Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]
Infusion-related cautions	Although rare, anaphylactoid reactions may require immediate emergency treatment with epinephrine, oxygen, IV steroids, antihistamines, pressor amines, and airway management.[2]
Dosage	Safety and effectiveness in pediatric patients below the age of 18 years have not been established.[2] **Children 8–11 years of age:** In a phase II clinical trial approximately 2.4 mg/kg/day divided q 12 hr was recommended.[4] **Children ≥12 years of age:** 1.5 mg/kg as a single dose (maximum: 100 mg/dose) followed by 2 mg/kg/day (maximum: 50 mg/dose) divided q 12 hr.[5] A loading dose of 3 mg/kg, followed by 6 mg/kg/day divided q 8 hr was successfully used in combination with daptomycin in a 21-month old with *Enterococcus faecium* meningitis.[6]
Dosage adjustment in organ dysfunction	No dosage adjustment is necessary in renal impairment or mild-to-moderate hepatic impairment (Child Pugh A and Child Pugh B).[2] Patients with severe hepatic impairment (Child Pugh C) should be treated with caution. The initial dose should be 100 mg followed by a reduced maintenance dose of 25 mg q 12 hr in *adults.*[2]
Maximum dosage	Initial dose of 100 mg and 50 mg/dose thereafter.[2]
Additives	None.

Tigecycline

Suitable diluents	NS, D5W.[2,7]
Maximum concentration	<1 mg/mL.[2,7]
Preparation and delivery	**Stability:** Reconstituted solution should be a yellow-orange color.[2,7]
IV push	Not used.
Intermittent infusion	30–60 minutes.[2,7]
Continuous infusion	Not used.
Other routes of administration	None.
Comments	**Rare adverse effects:** Tigecycline is structurally similar to tetracycline-class antibiotics and may have similar adverse effects including photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia).[2] Pancreatitis is a known adverse effect of the tetracyclines and has also been reported with tigecycline[2,8,9] There is a case report in a 9-year-old child.[10] **Monitoring:** The manufacturer recommends that prothrombin time or other suitable anticoagulation test should be monitored in those given warfarin.[2] Monitor patients periodically for abnormal liver function and observe for diarrhea.

Tissue Plasminogen Activator (t-PA)-Alteplase

Brand names

Activase, Cathflo Activase

Medication error potential

ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1]

Look-alike, sound-alike drug names.

ISMP reports that Activase has been confused with TNKase.[2]

USP reports that alteplase has been confused with TNKase. Activase has been confused with Retavase and TNKase.[3]

Contraindications and warnings

Contraindications[4]

In patients with acute myocardial infarction or pulmonary embolism, the following are contraindications: Active internal bleeding; history of a cerebrovascular accident; recent intracranial or intraspinal surgery or trauma; intracranial neoplasm, arteriovenous malformation or aneurysm; known bleeding diathesis; or severe uncontrolled hypertension.

In patients with acute ischemic stroke, the following are contraindications: Evidence of intracranial hemorrhage; suspicion of subarachnoid hemorrhage; intracranial or intraspinal surgery, serious head trauma or stroke within 3 months; history of intracranial hemorrhage; uncontrolled hypertension; seizure at stroke onset; active internal bleeding; intracranial neoplasm, arteriovenous malformation or aneurysm; known bleeding diathesis including but not limited to concomitant oral anticoagulants with international normalized ratio >1.7; heparin within previous 48 hours with activated partial thromboplastin time (aPTT) above baseline at presentation; or platelet count $<100 \times 10^9$/L.

Warnings: Bleeding is the most common complication.[4] Before thrombolytic therapy is used, clinicians should correct other concurrent hemostatic problems, such as thrombocytopenia or vitamin K deficiency.[5]

Infusion-related cautions

Extravasation can cause ecchymosis and inflammation.[4] The infusion should be stopped and local treatment applied.

Dosage

Recommendations for use of thrombolytics in pediatrics[5]

Neonates with a major vessel occluded and perfusion of limbs or vital organs that are being compromised: If thrombolytics are needed, plasminogen (fresh frozen plasma) should be given prior to infusion.

Children with venous thromboembolism: Thrombolysis is recommended only for life- or limb-threatening thrombosis. If it is used and plasminogen deficiency is present, plasminogen should be supplemented.

Bilateral renal vein thrombosis with renal impairment: Options include initial anticoagulation with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), or t-PA followed by UFH/LMWH.

Neonates with blocked central venous access devices (CVADs): Local thrombolysis after appropriate clinical assessment.

Infants and children with blocked CVADs: Thrombolytic should be used to restore patency. A second dose may be instilled if the catheter remains blocked after the first instillation.

Children with limb-threatening or organ-threatening femoral artery thrombosis who fail initial UFH therapy: Thrombolysis.

Tissue Plasminogen Activator (t-PA)-Alteplase

Dosage *(cont.)*

Neonates and children with symptomatic peripheral artery catheter-related thromboembolism: Unfractionated heparin with or without thrombolysis or surgical thrombectomy.

Systemic thrombolytic therapy: 0.1–0.6 mg/kg over 10–20 minutes (if a bolus is desired)[6–8] followed by infusion of 0.02–0.6 mg/kg/hr.[6,9–20] Because of bleeding tendencies in 50% of patients, some suggest that initial doses of 0.1 mg/kg/hr be increased gradually up to 0.5 mg/kg/hr if clot dissolution does not occur at lower doses.[10,11,21] Another suggests 0.5 mg/kg/hr for 1 hour followed by 0.25 mg/kg/hr for 4–11 hours until clot lysis occurs; however, the incidence of bleeding was still approximately 50% with the lower infusion rate.[19] Two studies reported that continuous infusion for 8–11 days in neonates did not result in resolution of the thrombus and was associated with bleeding.[22,23]

One case report described the successful use of 2.5 mg given in repeated small boluses, intra-arterially for thrombolysis of middle cerebral artery occlusion.[24]

A 2-year-old with a superior vena cava thrombus was treated successfully with 0.03 mg/kg/hr for 48 hours in combination with LMWH.[25] A 22-month-old with superior vena caval thrombosis received 1.5 mg/kg over 2 hours once daily for 2 days, after failing initial therapy with UFH.[26]

Three infants with brachial artery thrombosis and significant hand ischemia received UFH and intra-arterial t-PA (0.05 mg/kg).[27]

Local instillation of low-dose (0.01–0.06 mg/kg/hr) was effective in 12 of 17 children with acute thrombosis.[28]

Catheter occlusion

CVAD occlusion: Current manufacturer recommendations: (patients ≥30 kg) 2 mg in 2 mL; (patients <30 kg) 110% of internal lumen volume of catheter, not to exceed 2 mg/2 mL.[29] If patency is not restored after 120 minutes, a second dose may be administered.[29] Many dosing regimens have been reported in the literature. Depending on catheter volume, 0.5–2 mg (solution of 1 mg/mL) for a dwell time of 20 minutes to 4 hours.[30–39] Some catheters may require more than one instillation.[30,31,33,35–37,39]

Continuous infusions have been reported for hemodialysis catheter salvage: 2.5 mg in 25 mL NS (children)[40] or in 50 mL NS (*adults*)[41] infused into the hemodialysis catheter over 2–3 hours successfully restored patency in 91% of catheters.

Peritoneal catheters: 2 mg in 8 mL NS was infused via IP catheter to aid in drainage of abdominal abscesses in a 4-week-old infant.[42] To clear peritoneal dialysis catheter occlusions, a case series of six patients ages 3 weeks to 15 years old reported using 2 mg in 40 mL NS instilled for 1 hour then aspirated; this approach was successful in four of seven attempts.[43] A newborn received 4 mL of a solution of 1 mg/mL as a dwell for 2 hours to clear a peritoneal dialysis catheter. This approach was successful on two different occasions and prevented surgical catheter replacement.[44]

Glaucoma or cataract surgery complicated by hyphema and/or fibrin: Intracameral injection of 5–25 mcg postoperatively.[45–47] An additional dose may be required.[47]

Myocardial infarction: A 7-year-old child with a thrombosed coronary aneurysm was given 5 mg IV push <1.5 hours after arrival, followed by 0.75 mg/kg over 0.5 hour, then 0.5 mg/kg over 1 hour and symptoms resolved.[48]

Intrapleural fibrinolysis: For the treatment of complicated parapneumonic effusions or empyemas in infants as young as 3 months and children, the most common regimens included 0.1 mg/kg up to a max of 6 mg diluted in 25–100 mL NS[49] or alternatively a standard dose of 4 mg diluted in 30–50 mL NS.[50,51] The dose was instilled into the chest tube and the tube was clamped for 1 hour then returned to suction.[49–51] Multiple doses were often required, ranging from 1–7 doses per patient.[49–51]

Intrapericardial fibrinolysis: In a 4-month-old with a fibropurulent pericardial effusion due to *Staphylococcus aureus*, 1 mg in 5 mL NS was instilled via the pericardial drain, clamped for 2 hours (during which the patient was rotated side-to-side q 15 min), then was unclamped and allowed to drain. The dose was repeated 12 hours after the

Tissue Plasminogen Activator (t-PA)-Alteplase

Dosage *(cont.)*	initial dose and again the next day. Of note, the initial dose was intended to be a higher volume, but the patient experienced significant hemodynamic instability after 8 mL had been instilled; 2 mL were withdrawn thereby alleviating the symptoms. Caution must be exercised when administering doses via this method. This patient experienced complete resolution of the effusion 48 hours after starting therapy.[52] **Infective endocarditis:** Seven high-risk infants with overwhelming sepsis were treated with 0.2–0.3 mg/kg/hr × 6 hours with the dose then increased to 0.5 mg/kg/hr and continued until vegetations were no longer visible by echocardiogram.[53]
Dosage adjustment in organ dysfunction	None needed for renal dysfunction.[54] However, caution should be exercised in patients with hemostatic defects that might be related to renal or hepatic disease.[4]
Maximum dosage	100 mg in *adults*.[4]
Additives	Contains arginine and polysorbate 80.[4,55] (See Appendix C for information about polysorbate adverse effects.)
Suitable diluents	D5W, NS.[4]
Maximum concentration	1 mg/mL.[4,55]
Preparation and delivery	Reconstitute with provided SW.[4] Swirl the vial instead of shaking to avoid excessive foaming. Dilutions <0.5 mg/mL may result in precipitation.[55,56] However, concentrations 0.05–0.1 mg/mL have been used for infusions of 1–3 hours without reported incidence of precipitation.[40,41,43]
IV push	Not indicated.
Intermittent infusion	0.5–1 mg/mL. May be infused over several hours. Duration of infusion depends on response.[4]
Continuous infusion	0.5–1 mg/mL. Duration of infusion depends on response.[4]
Other routes of administration	Not indicated.
Comments	50 mg = 29 million International Units.[4] **Monitoring:** Fibrinogen <100 mg/dL suggests the need for cryoprecipitate or plasma replacement. The aPTT may not be useful for monitoring t-PA. The presence of fibrin degradation products or D-dimers may be helpful in determining if fibrinolysis is occurring. Maintain platelet count >100 × 10^9/L during thrombolysis.[5] **Significant adverse events:** Bleeding is the most common adverse effect.[4] In *adults* receiving intrapleural t-PA, concomitant therapeutic anticoagulation, but not prophylactic anticoagulation, was associated with a higher risk of hemorrhage.[57] In children bleeding from venipuncture sites, extension of intraventricular hemorrhage, bruising, and other internal bleeding have been reported.[6,8,11,19,21]

Tissue Plasminogen Activator (t-PA)-Alteplase

Comments *(cont.)*

Two infants with fulminant meningococcemia made a full recovery after being given 0.5 mg/kg/hr for 1–1.5 hours followed by 0.25 mg/kg/hr for 1.5–4 hours.[58] Later these authors conducted a retrospective review of 62 infants with meningococcal purpura fulminans treated with a median dose of 0.3 mg/kg/hr (range: 0.008–1.13 mg/kg/hr) for a median duration of 9 hours (range of 1.2–83 hours) and found that 29 (47%) patients died, 17 (51%) of the 33 survivors had amputations, and five patients (8%) experienced intracranial hemorrhage. Authors questioned the use of t-PA in patients with this disease.[59]

Mild bleeding can be treated with localpressure and supportive care. Major bleeding may be treated by stopping t-PA; administering cryoprecipitate (usual dose 1 unit/5 kg or 5–10 mL/kg), an antifibrinolytic, or both; and administering other blood products as indicated.[5]

Tobramycin Sulfate

Brand names

Generic

Medication error potential

USP reports confusion with gentamicin and vancomycin.[1]

Contraindications and warnings

U.S. boxed warning: Patients with impaired renal function and those receiving large doses or prolonged therapy have an increased risk for nephrotoxicity and ototoxicity (i.e., vestibular and auditory), of which ototoxicity may be irreversible.[2,3] The risk of toxicity can also be increased by prolonged elevations in serum concentrations; concurrent use of medications known to be nephro-, neuro-, or oto-toxic; dehydration; and advancing age.[2,3] (See Rare Adverse Effects and Monitoring in the Comments section.)

Contraindications: Known hypersensitivity reaction to tobramycin or other aminoglycosides.[2]

Other warnings: Aminoglycosides can cause neuromuscular blockade and potentiate the effects of neuromuscular blockers.[2,4,5] If neuromuscular blockade occurs, calcium salts may reverse it.[2] (See Appendix C for specific information.)

Infusion-related cautions

None.

Dosage

Although questioned in pediatric patients the following equation is recommended in *adult* obese patients[2,6,7]:

Dosing weight = IBW + 0.4 (TBW – IBW). (See Appendix B.)

Loading dose: Limited data are available, but some practitioners advocate an initial 3–5 mg/kg dose in neonates and infants.[8–14]

Neonates

Maintenance dose: Many studies using various dosing methods for aminoglycosides have been reported in neonates. Most reports have based recommendations on either weight and postnatal age (PNA)[15–21] or gestational age.[13,14,22–36] Use of dose and interval equations based on AUC have also been recommended in the preterm neonate.[37–40] Traditional dosing (2.5 mg/kg/dose) in premature neonates has become less commonly recommended with large dose, extended interval regimens becoming accepted practice**.** PNA at which any of these regimens are applicable has not been well studied, but the few studies delineating a PNA have generally been ≤7 days of age.[13,19,22,23,25–28,31,33,34,37]

Based on age and weight

	<7 days	**≥7 days**	
<1200 g	**≥1200 g**	**1200–2000 g**	**>2000 g**
2.5 mg/kg q 16–24 hr[15–17]	2.5 mg/kg q 12 hr[17]	2.5 mg/kg q 8–12 hr[17]	2.5 mg/kg q 8 hr[17]
OR			
5 mg/kg q 48 hr[18,19,21]	4.5–5 mg/kg q 24–48 hr[18–21]	5 mg/kg q 24 hr[18,20]	

Dosage *(cont.)*

Based on weeks gestational age (WGA)

<30 WGA	30–34 WGA	>34 WGA
2.5–3 mg/kg q 18–36 hr[14,31–35]	2.5–3 mg/kg q 16–24 hr[14,31–34,36]	2.5 mg/kg q 12–24 hr[14,31–34]
OR		
4–5 mg/kg q 36–48 hr[25,28–30]	4–5 mg/kg q 24–48 hr[25,29,30]	4 mg/kg q 24 hr[13,22–27]

Infants and children: 7.5 mg/kg/day divided q 8 hr.[2,17]

Once-daily dosing outside the neonatal period: Several investigators have reported that once-daily dosing has comparable efficacy and perhaps less toxicity than classical 8–12 hours dosing.[13,41] A single dose of *aminoglycoside* has been given once daily (over 20–30 minutes) in critically ill infants and children with severe gram-negative infections,[42–44] bone marrow transplantation,[45] or in febrile neutropenic patients with cancer.[46–51] At this time, the use of once-daily dosing in infants and children is controversial.[52] The most recent edition of the *American Academy of Pediatrics Red Book: Report of the Committee on Infectious Diseases* continues to recommend 2.5 mg/kg/dose administered in multiple daily doses in all age groups and states that once-daily dosing is investigational in children.[17]

Cystic fibrosis: Patients require larger doses due to increased clearance and volume of distribution. The traditional dose is 10 mg/kg/day divided q 8 hr[53]; however, doses have ranged from 7.5–20 mg/kg/day divided q 8 hr.[53] Although several once-daily regimens have been reported in pediatric cystic fibrosis patients, 10 mg/kg/day has become the preferred regimen.[54] Based on limited evidence, The Cystic Fibrosis Foundation recently recommended once-daily dosing of 10 mg/kg/day for all ages.[55]

Dosage adjustment in organ dysfunction

If CrCl is >50 mL/min, give a normal dose q 8 hr; if CrCl is between 30–50 mL/min, give a normal dose q 12–18 hr; if CrCl is between 10–29, give normal doses q 18–24 hr; and if CrCl is <10 mL/min, give a normal dose q 48–72 hr.[56]

Maximum dosage

Larger doses or shorter dosing intervals are sometimes required in patients with cystic fibrosis,[53] major thermal burns or dermal loss,[57] ascites, or in patients with febrile granulocytopenia.[46–51] Based on similarities between aminoglycosides, prolonged dosing interval may be required in those receiving extracorporeal membrane oxygenation.[58]

Additives

The premixed product contains 15.4 mEq of sodium/100 mL.[59] The 1.2 g/30 mL vials contain 23.5 mg (1.02 mEq) sodium and the 80 mg/2 mL vials contain 1.6 mg (0.07 mEq) of sodium.[2] Contains sodium bisulfite.[2,59] (See Appendix C for specific information about sulfite hypersensitivity.)

Suitable diluents

D5W, NS.[2,59]

Maximum concentration

4 mg/mL.[59] The volume must allow accurate measurement and delivery over 30 minutes.

Preparation and delivery

Delivery system issues: The mixing of tobramycin with a beta-lactam antibiotic in vitro can result in substantial inactivation of the aminoglycoside.[59] (See Appendix C for more specific information.)

Compatibility: See Appendix D for PN compatibility information.[60]

Tobramycin Sulfate

IV push	Not recommended. Aminoglycosides have been safely administered by rapid IV push (over 3–5 minutes)[61–64]; however, ototoxicity has been associated with elevated aminoglycoside peak serum concentrations following bolus administration in *adults*.[65]
Intermittent infusion	4 mg/mL or dilute in appropriate volume of D5W or NS to allow more accurate dosage measurement and infusion over 20–60 minutes.[59]
Continuous infusion	Not recommended. Toxicity occurs more frequently, and the value of this administration method compared to intermittent infusion has not been established.[65–67]
Other routes ofadministration	40 mg/mL may be given IM.[59] Solutions prepared from or commercially available in bulk packages, ADD-Vantage vials, and premixed solutions in NS should not be given IM.[59]
Comments	**Rare adverse effects:** Aminoglycosides accumulate in renal cortical tissue and may damage proximal tubule cells leading to oliguric renal failure. Risk of nephrotoxicity may be influenced by type of aminoglycoside, dose, duration (cumulative dose), frequency of therapy and elevated serum concentration.[2] It is also increased by advancing age, pre-existing renal or hepatic dysfunction, decreased renal perfusion, hypoalbuminemia, and dehydration.[2,3] Current administration of nephrotoxic medications may increase the risk of toxicity and should be avoided.[2] Cochlear and/or vestibular ototoxicity has been associated with all aminoglycoside antibiotics.[4] Total AUC is a better indicator of ototoxic risk than either peak or trough serum concentration.[68,69] Use cautiously when giving with other drugs (e.g., loop diuretics, platinum-based chemotherapeutic agents) known to cause ototoxicity. Aminoglycosides may potentiate the curare-like effects on the neuromuscular junction and should be used cautiously in patients with neuromuscular disorders since they may aggravate muscle weakness.[2,4,5] Tetany and muscle weakness have been described in infants. Aminoglycosides may enhance the respiratory depressant effect of neuromuscular-blocking agents and may prolong blockade.[2,70,71] **Monitoring:** Because large variability exists in patient response to therapy, individualize dosage based on serum concentrations, clinical response, and renal function. Recommended peak and trough serum tobramycin concentration are 4–12 mg/L and $<$2 mg/L, respectively. Desired peak concentrations are dependent on the site of infection. Although serum concentration monitoring has become routine practice in many institutions, not all patients require monitoring.[72,73] **Drug interactions:** Consult appropriate resources before combining any drug with tobramycin. **Laboratory interference:** Serum concentrations may be falsely elevated when blood samples are collected through central venous Silastic catheters.[74]

Topotecan HCl

Brand names	Hycamtin
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that topotecan has been confused with irinotecan; no patient harm resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** Must be administered under the supervision of an experienced physician. Topotecan may cause severe bone marrow suppression, primarily neutropenia, and should not be administered to patients with baseline neutrophil counts $<$1500 cells/mm^3. Monitor blood counts before and during therapy.[3] (See Monitoring in the Comments section.) **Contraindications:** Should not be used in patients with a history or known hypersensitivity to topotecan or any of the components. Should not be used in pregnant or breastfeeding patients or those with severe bone marrow suppression.[3] **Other warnings:** May also cause thrombocytopenia and anemia.[3] (See Monitoring in the Comments section.)
Infusion-related cautions	Extravasation, causing mild reactions such as erythema and bruising, has been reported.[3,4] See Appendix E for additional information regarding extravasation treatment.
Dosage	Consult institutional protocol for complete dosing information. Topotecan is a component of combination therapy or as single agent therapy to treat multiple pediatric solid tumors, including osteosarcoma, neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, retinoblastoma, ependymoma, as well as pediatric leukemia. **Combination therapy for solid tumors:** 0.75 mg/m^2/day over 30 minutes for 5 days; repeat q 21 days.[5] **Single agent therapy for refractory solid tumors:** 1.4–2.4 mg/m^2/day over 30 minutes for 5 days; repeat q 21 days.[6–8] **Pediatric solid tumors:** 1 mg/m^2/day (range: 0.6–1.9 mg/m^2/day) for 3 days as a continuous infusion; repeat q 21 days[9,10] or over 30 minutes 5 days a week for 2 consecutive weeks; repeat q 24–28 days.[11] **Pediatric refractory acute leukemias:** 2.4 mg/m^2/day over 30 minutes for 9 days; repeat q 21 days.[12,13]
Dosage adjustment in organ dysfunction	No dosage adjustment necessary in patients with hepatic dysfunction or mild renal impairment (CrCl 40–60 mL/min).[3] One reference recommends that patients with moderate renal failure (CrCl 20–39 mL/min) receive 50% of the standard dose.[14] Another reference recommends a 25% dose reduction for patients with CrCl $<$50 mL/min, a 50% reduction for CrCl of 10–50 mL/min, and a 75% reduction with CrCl $<$10 mL/min.[15]
Maximum dosage	Not established. One *adult* patient received a single dose of 35 mg/m^2 and developed reversible severe neutropenia.[3]
Additives	None.
Suitable diluents	Reconstitution with SW; further dilution with D5W or NS.[3,4]

Maximum concentration	0.5 mg/mL.[14]
Preparation and delivery	Do not dilute in alkaline solutions.[4]
IV push	Not recommended.
Intermittent infusion	Dilute reconstituted drug (1 mg/mL) in 50–250 mL D5W or NS and infuse over 30 minutes.[3,4]
Continuous infusion	Has been administered via continuous infusion for up to 72 hours.[10]
Other routes of administration	Periocular, intra-arterial topotecan has been used for treatment of retinoblastoma.[16,17] IT doses have been used in pediatric patients with refractory leptomeningeal leukemia.[18]
Comments	**Significant adverse effects:** Topotecan is associated with a low (10% to 30%) risk of emesis.[19] Patients should receive antiemetic therapy to prevent acute and delayed nausea and vomiting. The recommended therapy is a corticosteroid on every day chemotherapy is administered; alternatives are a phenothiazine (e.g., prochlorperazine) or a butyrophenone (e.g., droperidol).[19,20] Therapy for delayed nausea and vomiting is generally not needed. Breakthrough medications should also be offered. Selection should be based on what the patient is currently receiving for acute emesis prophylaxis. **Monitoring:** Monitor CBC with platelets, renal function, and bilirubin.[3,14] Patients should have a baseline absolute neutrophil count >1500 cells/mm^3 and a platelet count >100,000 cells/mm^3 before drug administration.[3] The manufacturer recommends dose adjustments with severe neutropenia or thrombocytopenia.[3] (See Contraindications and Warnings section.) **Drug interactions:** BCRP/ABCG2 inhibitors (e.g., filgrastim, denosumab, platinum derivatives) may increase serum concentrations of topotecan.[14] Consult appropriate resources for dosing recommendations before combining any drug with topotecan.

Tranexamic Acid

Brand names	Cyklokapron, generic
Medication error potential	Cyklokapron may be confused with cycloSPORINE.[1]
Contraindications and warnings	**Contraindications:** Patients with acquired defective color vision (due to inability to monitor for toxicity), patients with subarachnoid hemorrhage, patients with active intravascular clotting, and patients with hypersensitivity to the drug or any ingredient.[2] **Warnings:** Focal retinal degeneration has developed in animals at doses ranging from 3–40 times the recommended human dose. Although retinal changes have not been reported in humans, vision changes have been reported. The manufacturer recommends ophthalmological exam before and regularly during treatment for patients who are to receive tranexamic acid continually for more than several days.[2] Convulsions have been reported.[2] Venous and arterial thrombosis or thromboembolism has been reported.[2]
Infusion-related cautions	Hypotension may occur with rapid infusion; administer at a maximum rate of 100 mg/minute.[2]
Dosage	**Reduction of blood loss during and after congenital heart disease repair** **Neonates:** Bolus dose of 100 mg/kg after induction of anesthesia,[3,4] either with[3] or without[4] an additional dose of 100 mg/kg into the cardiopulmonary bypass circuit, then followed by a continuous infusion of 10 mg/kg/hr during the operation[3,4] has been used in neonates. A lower dose (50 mg/kg as a slow infusion just prior to surgical incision)[5] has also been studied in neonates but was found to reduce blood loss only in patients with cyanotic heart disease or those undergoing a second thoracotomy. **Infants, children, and adolescents:** In patients undergoing repair of cyanotic heart defects, the following regimens have been reported. Initial doses (after anesthesia induction) of 10 mg/kg,[6–8] 50 mg/kg[5,9] or 100 mg/kg,[4,10,11] with a dose into the cardiopulmonary bypass circuit of 10 mg/kg[6–8] or 100 mg/kg,[10,11] then followed either by a continuous infusion of 1 mg/kg/hr for 8 hours[6] or 10 mg/kg/hr during the operation.[4,11] Instead of a continuous infusion, some centers reported an additional bolus dose at the end of bypass (10–20 mg/kg,[6–8] 50 mg/kg,[9] or 100 mg/kg[10]). Each of these studies reported efficacy versus placebo, or similar efficacy compared to aprotinin (no longer available on the U.S. market.) In patients undergoing repeat thoracotomy, initial dose of 100 mg/kg with 100 mg/kg into the cardiopulmonary bypass circuit and 10 mg/kg/hr until transfer to the ICU reduced blood loss and transfusion requirements compared to placebo.[11] **Reduction of blood loss during and after craniofacial surgery:** Loading dose 15–100 mg/kg over 15–20 minutes followed by 5–10 mg/kg/hr during surgery was associated with reduced blood loss and/or reduced transfusion requirements in two randomized, double-blind trials[12,13] and one retrospective study.[14] **Reduction of blood loss during and after spine surgery:** Loading dose 10–100 mg/kg (one study limited the loading dose to 2 g in *adults*)[15–18] over 15 minutes[17,18] followed by 1–10 mg/kg/hr (one study limited the infusion to 100 mg/hr in *adults*) during surgery[16–18] or continued 5 hours after surgery[15] was associated with reduced blood loss and/or reduced transfusion requirements in three randomized, double-blind trials[15,17,18] and one retrospective study.[16]

Dosage *(cont.)*	**Reduction of blood loss during surgery in heparinized patients:** One study of 10 patients reported the use of tranexamic acid 4–10 mg/kg initial dose with 2 mg/kg/hr for 24–48 hours (one patient received 15 mg/kg/dose q 8 hr for 48 hours) in patients undergoing surgical repair of congenital diaphragmatic hernia (CDH) while heparinized (activated clotting times 180–200 seconds) and receiving extracorporeal membrane oxygenation (ECMO). Authors reported reduced blood loss and transfusion requirement compared to historical patients who did not receive tranexamic acid.[19] Another study also reported on the use of tranexamic acid during and after surgical repair of CDH in patients on or off ECMO. The typical regimen was a loading dose of 4 mg/kg 1 hour before surgery followed by 1 mg/kg/hr for 24 hours postoperatively.[20] **Tooth extraction in patients with hemophilia:** 10 mg/kg immediately before extraction (together with replacement therapy), and 10 mg/kg/dose q 6–8 hr short-term (2–8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.[2]
Dosage adjustment in organ dysfunction	**Manufacturer recommendations (based on dosing for tooth extraction) for dosing adjustment in impaired renal function, *adults*[2]** **SCr 1.36–2.83 mg/dL:** IV 10 mg/kg BID. **SCr 2.83–5.66 mg/dL:** IV 10 mg daily. **SCr >5.66 mg/dL:** IV 10 mg/kg q 48 hr or 5 mg/kg daily. **Alternatively** **CrCl >50 mL/min, *adults*:** 50% of the usual dose.[21] **CrCl 10–50 mL/min, or receiving continuous renal replacement therapy (CRRT), *adults*:** 25% of the usual dose.[21] **CrCl ≤10 mL/min, *adults*:** 10% of the usual dose.[21] Avoid in patients undergoing intermittent hemodialysis or peritoneal dialysis.[21]
Maximum dosage	Single doses of 100 mg/kg.[3,4,10,11] Continuous infusion of 10 mg/kg/hr.[3,4,11]
Additives	None.
Suitable diluents	Not specified. (See Compatibility in the Preparation and Delivery section.)
Maximum concentration	100 mg/mL.[2]
Preparation and delivery	**Compatibility:** May be mixed with most solutions such as electrolyte, carbohydrate, amino acid, and dextran solutions.[2]
IV push	≤100 mg/mL (commercially available) over at least 1 minute.[2]
Intermittent infusion	≤100 mg/mL. Doses have been infused over 15 minutes,[11–13] 20 minutes,[14] or 30 minutes[6] in some studies.

Tranexamic Acid

Continuous infusion	≤100 mg/mL.
Other routes of administration	Not indicated.
Comments	**Significant adverse effects:** Whether tranexamic acid, when used to reduce blood loss in pediatric cardiac surgery, is more prone to adverse effects including renal insufficiency or seizures compared to similar agents such as aminocaproic acid or aprotinin (no longer available on the U.S. market), is controversial. A large multicenter analysis including over 20,000 patients[22] suggested that tranexamic acid had more favorable outcomes compared to aprotinin (in-hospital mortality, bleeding requiring surgical intervention, ICU length of stay, and the requirement for dialysis). Conversely, a single-center study reported better clinical outcomes for aprotinin compared to tranexamic acid (better hemostasis, reduced inotropic requirement, and shorter duration of mechanical ventilation) without any increase in thrombotic events or acute kidney injury.[3] One group found a trend toward increased seizures in patients receiving tranexamic acid compared to aprotinin (n = 4 patients versus 0 patients, respectively; P = .14). The same group reported a retrospective analysis that found no difference in safety outcomes (renal failure or seizures) between patients receiving tranexamic acid or aminocaproic acid.[23] **Drug interactions:** Administration with Factor IX Complex concentrates or anti-inhibitor coagulant concentrates may increase the risk of thrombosis; this combination should be avoided.[2]

Tromethamine

Brand names	THAM
Medication error potential	Look-alike, sound-alike drug names. ISMP reports that tromethamine may be confused with Trophamine.[1]
Contraindications and warnings	**Contraindications:** Uremia and anuria.[2] Also contraindicated in neonates with chronic respiratory acidosis and salicylate intoxication.[2] **Warnings:** Hypoglycemia can occur in preterm and term neonates.[2]
Infusion-related cautions	Extravasations may result in tissue necrosis, severe inflammation, and sloughing.[2–5] Extravasations may be treated with procaine 1% added to hyaluronidase or with phentolamine infiltrated around the site.[3] For infusion by peripheral vein, an indwelling catheter in a large vein in an elevated limb is recommended to minimize irritation.[2] Infusion via low-lying umbilical catheters may result in hepatocellular necrosis.[2] (See Comments section.) Rapid infusion may result in prolonged hypoglycemia.[2] Three of four *adults* given tromethamine to evaluate its effects on blood chemistries experienced decreases in blood glucose, which resulted in persistent symptoms for 24 hours in one *adult*.[6] Too rapid administration may decrease the respiratory drive resulting in respiratory depression and apnea.[7]
Dosage	Doses (mL) are based on 0.3 M solution; 100 mL = 3.6 g, 30 mEq, 30 mmol.[2] **Neonates with acidosis associated with respiratory distress syndrome:** 1 mL/kg for each pH unit <7.4.[2,8] One study reported using doses of 1.8–4.7 mmol/kg in six neonates (26–37 weeks gestational age [WGA]).[9] **Infants and children:** Dose (mL) = base deficit (mEq/L) × body weight (kg) × 1.1[2]
Dosage adjustment in organ dysfunction	Contraindicated in patients who are anuric or uremic.[2]
Maximum dosage	In neonates, the maximum dose is 5–7 mmol/kg/day.[4] In *adults*, 35 g (291 mmol)/hr[2] or 15 mmol/kg/day.[4,10]
Additives	Glacial acetic acid is added to decrease the pH to 8.6.[2] The buffering capacity is decreased about 10% with this addition.[2]
Suitable diluents	None noted.
Maximum concentration	Undiluted.[2]
Preparation and delivery	Vials do not contain preservatives and are intended for single use.[2]
IV push	Not indicated.

Intermittent infusion	Over >1 hour.[2] In acute acidosis, 25% to 50% of the calculated deficit can be given over 5–10 minutes with the remainder infused over >1 hour.[4,5]
Continuous infusion	Not given continuously.
Other routes of administration	Not indicated.
Comments	**Significant adverse effects:** Postmortem evaluation of 67 neonates (24–38 WGA) given 1.2 M tromethamine or sodium bicarbonate via umbilical vein reported hemorrhagic liver necrosis in 22 (32.8%).[11] Bladder necrosis has also been reported with tromethamine was infused via umbilical vein.[4] Of note, in these reports the tromethamine used was unbuffered and had a pH >10. Use of buffered tromethamine with a pH of ~8.6 does not seem to result in these adverse effects.[4] Irreversible ischemia of the hand was reported in an *adult* receiving unbuffered THAM 3.6% (pH 10.5) peripherally.[12] This product is not available in the United States.

Valproate Sodium

Brand names

Depacon

Medication error potential

None reported.[1]

Contraindications and warnings

U.S. boxed warning

Hepatic failure: Fatalities have occurred in patients receiving valproic acid and its derivatives.[2] Because of their increased risk for hepatotoxicity, valproate should be used cautiously in children <2 years of age, especially if they are receiving multiple anticonvulsants, have congenital metabolic disorders, severe seizures accompanied by mental retardation, or organic brain disease.[3–6]

Pancreatitis: Life-threatening pancreatitis has been reported in both children and *adults* and has occurred shortly after initial use and after several years of use.[2,7–9] Some patients have developed hemorrhagic pancreatitis that progressed rapidly from onset of symptoms to death. If pancreatitis is diagnosed, valproate should be discontinued.

Teratogenicity: Congenital malformations such as neural tube defects (e.g., spina bifida) have been reported.[2]

Contraindications: Should not be administered to patients with hepatic disease or significant hepatic dysfunction. It is contraindicated in patients with known hypersensitivity to the drug and should not be given to patients with known urea cycle disorders.[2]

Other warnings: Thrombocytopenia, hypothermia, and hyperammonemia may occur.[2] (See Rare Adverse Effects for information on suicide in the Comments section.)

Infusion-related cautions

Severe vein irritation and pain at the injection site may occur following administration of undiluted solution.[2] Compartment syndrome has been reported in an *adult.*[10]

Dosage

IV use for >14 days has not been studied.[2] Convert to oral administration as soon as possible.

Headache: IV valproate has been safely and effectively used in *adults*[11–13] and adolescents.[14] Initial doses of 1000 mg were infused at 50 mg/min in 31 adolescents.[14] When response was not sufficient, a second 500 mg/dose was given.[14] In another study, patients were given a loading dose of 20–40 mg/kg followed by a continuous infusion of 1–1.5 mg/kg/hr.[15]

Seizures (acute, nonstatus epilepticus)

Replacement therapy: Individuals chronically receiving oral valproate may be converted to IV valproate using the same total daily dose (1:1 conversion); however, it should be administered q 6 hr or by continuous infusion.[2]

Children (≥2 years) and adolescents: 10–15 mg/kg administered q 6 hr; for chronic therapy increase weekly by 5–10 mg/kg/day until seizures are controlled, therapeutic concentrations are reached, or the patient exhibits unacceptable toxicities.[2,16–21] Some have given a loading dose of 20–40 mg/kg followed by a continuous infusion of 1–1.5 mg/kg/hr.[15] Maintenance dose in children ≥2 years: 30–60 mg/kg/day divided q 6 hr.[15,17–20,22,23]

Seizures—generalize convulsive status epilepticus

Neonates and infants: Although IV valproate has been used safely in neonates to treat acute seizures and status epilepticus,[24,25] it should not be used unless all other options have failed. A single dose of 10–25 mg/kg was given and an apparent Vd of 0.245 L/kg and clearance of 25 mL/hr/kghr were estimated.[24] The elimination of valproate is significantly reduced in neonates and infants; therefore, doses may need to be administered less frequently than in older children. If used, it should be given with L-carnitine. (See Other in the Comments section.)

Dosage *(cont.)*	**Children ≥2 years and adolescents:** Loading dose of 13.4–40 mg/kg[15,26–30] or 500 mg.[30] The need for further loading doses should be guided by clinical response and serum concentrations. If the patient is on valproate monotherapy or other anticonvulsants that do not induce the cytochrome P450 system, begin with 1 mg/kg/hr; if the patient is on one or more inducers (e.g., phenobarbital, phenytoin, rifampin), begin with 2 mg/kg/hr; if the patient is receiving inducers and is in pentobarbital coma, begin with 4–6 mg/kg/hr.[25] One group recommends beginning at 5 mg/kg/hr; once the patient is seizure free for 6 hours, the dose should be reduced by 1 mg/kg/hr q 2 hr.[27] **Seizures—nonconvulsive status epilepticus** **Children ≥2 years and adolescents:** A loading dose of 13.4–25 mg/kg[22,26] followed by 4 mg/kg q 6 hr.[26] **Seizures—prophylaxis for post-traumatic epilepsy:** Because a clinical study in *adults* with head trauma showed a higher mortality rate than that observed for phenytoin, IV valproate is not recommended for seizure prophylaxis following head trauma.[2,31]
Dosage adjustment in organ dysfunction	No dosage adjustment necessary in renal dysfunction.[2,32] However, renal failure may cause a disproportionate increase in free-to-total valproate ratios, causing total serum concentrations to be misleading.[2,33] Should not be administered to patients with hepatic disease or significant hepatic dysfunction.[2]
Maximum dosage	Has not been established. A loading dose of 40 mg/kg[24] and a continuous infusion of 6 mg/kg/hr have been used in children.[23] A dose of 240 mg/hr has been given to a 67-year-old *adult*.[34] Children receiving one or more medications known to increase the metabolism of valproate may require doses up to 100 mg/kg/day, while children in pentobarbital coma may require larger doses (150 mg/kg/day).[25,35]
Additives	None reported.
Suitable diluents	The parenteral injection has been used undiluted; however, severe vein irritation occurred. Administer in a 1:1 or 2:1 dilution in at least 50 mL of D5W, NS, or LR.[2]
Maximum concentration	25–50 mg/mL.[2]
Preparation and delivery	**Stability:** When stored in glass or PVC bags at room temperature (15°C to 30°C) the product is stable for at least 24 hours.[2] Any unused portion of a vial should be discarded.[2]
IV push	Although not recommended by the manufacturer,[2] some have given as a bolus without adverse effects: loading dose of 20–40 mg/kg over 1–5 minutes[31]; one report gave 7.5–41.5 mg/kg at a rate of 1.5–11 mg/kg/min[36]; and 10 mg/kg/min and doses of up to 30 mg/kg.[37] (See Rare Adverse Effects in the Comments section.)
Intermittent infusion	60 minutes (but not more than 20 mg/min)[2,15] 1–6 mg/kg/min.[24,30] Others have given ≤15 minutes (8.2–15.4 mg/kg).[38] (See Rare Adverse Effects in the Comments section.)
Continuous infusion	2–4 mg/mL in D5W or NS at a rate of 1–6 mg/kg/hr.[2,25]

Valproate Sodium

Other routes of administration	None reported.

Comments

Rare adverse effects

Hepatic failure: See U.S. Boxed Warning in the Contraindications and Warnings section.

Hypotension and arrhythmia: The manufacturer's recommendation to infusion over 60 minutes is predicated on concerns about hemodynamic instability. An 11-year-old girl who received 30 mg/kg (480 mg) over 20 minutes (0.5 mg/kg/hr) developed significant, but reversible, hypotension 12 minutes into the infusion.[38] Another 11-year-old girl developed hypotension 20 minutes after receiving 30 mg/kg (960 mg) over 60 minutes.[30] Others have noted that 11 mg/kg/min[14] and 1.5–11 mg/kg/min[29,30,39–41] did not produce hypotension, bradycardia, or arrhythmias. In one clinical safety study, about 90 patients with epilepsy were given a single infusions of (up to 15 mg/kg and mean dose of 1184 mg) over 5–10 minutes (1.5–3.0 mg/kg/min).[2] Patients generally tolerated the more rapid infusions.[2]

Thrombocytopenia: About 25% of those given 50 mg/kg/day developed thrombocytopenia (platelet counts $<75 \times 10^9$/L).[2,42,43] The likelihood increases when total serum valproate concentrations exceed 100 mg/L.

Hyperammonemia: Despite normal liver function tests, hyperammonemic encephalopathy accompanied by unexplained acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting have been reported.[2] An ammonia level should be measured and valproate should be stopped if the level is elevated. Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone.[2,44]

Hypothermia (unintentional drop to <35°C): Has occurred in patients receiving valproate and those given concomitant topiramate with valproate.[2,45,46] It has been noted in patients with and without hyperammonemia.[2]

Suicidal behavior/ideation: The incidence of this adverse effect has been noted to be greater than placebo (0.43% versus 0.24% risk) in patients receiving 11 anticonvulsants (carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) as either monotherapy or as adjuvant therapy for the treatment of epilepsy, psychiatric disorders, and other conditions.[2] The FDA will require that the product labeling of the entire class of antiepileptics include a warning concerning the risk of suicidality.

Monitoring: Although dosing is often guided by total serum valproate concentrations (50–150 mg/L), the relationship between serum concentration and clinical response is not well documented. The variability in serum concentrations may be attributed to the nonlinear, concentration-dependent protein binding of valproate, which affects it clearance. Patients planning surgery should have platelet count and coagulation parameters monitored before surgery.[2]

Pharmacokinetics: Infants ≤2 months of age have a decreased ability to eliminate valproate compared to older children and *adults.* This is attributed to a combination of immature development of glucuronosyltransferase and other hepatic enzyme and an increased volume of distribution due to decreased plasma protein binding.[47] Pediatric patients (i.e., between 3 months and 10 years) have 50% higher clearances expressed on weight (i.e., mL/min/kg) than do *adults*.[18,19] Over the age of 10 years, children have pharmacokinetic parameters that approximate those of *adults*.[18,19]

Drug interactions: Because valproate inhibits CYP2C9, epoxide hydroxylase, and beta-oxidation, it is associated with numerous drug interactions.[48] Valproate can also serve as a substrate and can be inhibited or induced by other drugs. Consult appropriate resources for dosing recommendations before combining any drug with valproate.

Other: Some have advocated that the concomitant administration of L-carnitine may improve survival of those with severe valproate-induced hepatotoxicity. L-carnitine may enhance beta-oxidation of valproate, thereby limiting cytosolic omega-oxidation and the production of toxic metabolites that have been implicated in liver toxicity and ammonia accumulation.[49]

Vancomycin HCl

Brand names

Generic

Medication error potential

USP reports confusion with clindamycin, gentamicin, tobramycin, valacyclovir, vecuronium, and Vibramycin.[1]

Contraindications and warnings

Contraindications: Documented hypersensitivity to vancomycin or any of its components.[2] If possible, avoid in patients with previous severe hearing loss.[2]

Warnings: Rapid administration may cause exaggerated hypotension, including shock, and, rarely, cardiac arrest.[2]

Transient or permanent hearing loss has been reported in those given excessive doses of vancomycin, who have underlying hearing loss, or received therapy with other ototoxic agents.[2] (See Rare Adverse Effects in the Comments section.)

Use cautiously in renal insufficiency.[2] (See Dosage Adjustment in Organ Dysfunction section.)

Prolonged use may cause superinfection and/or *Clostridium difficile*–associated diarrhea (CDAD), which has been reported and may range in severity from mild diarrhea to fatal colitis.[2] If CDAD is suspected or confirmed, appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.[2]

Infusion-related cautions

Administration over <60 minutes may cause red man syndrome.[2] (See Rare Adverse Effects in the Comments section.) Concomitant administration with anesthetic agents has resulted in erythema histamine-like flushing and anaphylaxis.[2]

Thrombophlebitis can be minimized by using dilute solutions (e.g., 2.5–5 mg/mL) and rotating injection sites.[2] Extravasation should be avoided.[2] (See Appendix E for information regarding infiltration.)

Dosage

The following dosing recommendations are based on the traditional therapeutic range. Higher doses may be necessary to produce troughs ≥15 mcg/mL.[3] Some authors have recommended up to 85 mg/kg/day in children to reach these higher concentrations.[4]

Dose obese individuals using actual or total body weight.[5–8] Shorter dosing intervals may be needed to maintain trough serum vancomycin concentration above 5 mg/L.[7,8]

Neonates: Some advocate a loading dose of 15 mg/kg.[2,9]

Although a variety of neonatal dosing recommendations have been published,[10–14] the following continue to be the most common and are based on postnatal age (PNA) and weight.

Based on weight and PNA

PNA	<1200 g	1200–2000 g	≥2000 g
<7 days	15 mg/kg q 24 hr*[15,16]	20–30 mg/kg/day divided q 12–18 hr[15,16]	30–45 mg/kg/day divided q 8–12 hr[15]
≥7 days		30–45 mg/kg/day divided q 8–12 hr*[15]	40–60 mg/kg/day divided q 6–8 hr[15]

*Until 4 weeks of age.

Infants and children

Mild-to-moderate infections: 40 mg/kg/day divided q 6–8 hr up to 2 g/day.[15]

Severe infections (including meningitis and bacteremia): 60 mg/kg/day divided q 6 hr up to 4 g/day.[3,15] In *adults,* give loading dose of 25–30 mg/kg over at least 60 minutes followed by 45–60 mg/kg/day divided q 8–12 hr.[17]

Dosage *(cont.)*	Each dose should be administered no faster than 10 mg/min or over a period of at least 60 minutes, whichever is longer.[2] **Bacterial endocarditis (prophylaxis):** A single dose of vancomycin 30–60 minutes before the procedure may be indicated in the highest risk patients.[18] (See Comments section.) **Bacterial endocarditis (treatment):** Current guidelines recommend 60 mg/kg/day divided q 6 hr for 2–6 weeks depending on the source of infection.[3] However, other guidelines have recommended 40 mg/kg/day divided q 8–12 hr for 4–6 weeks for endocarditis with native or prosthetic valves in combination with other antibiotics.[19] **Central venous catheter infection:** 25 mg/L of vancomycin added to PN solution as a continuous infusion[20–22] or as a flush/lock.[23,24] Although this dose has been used for prophylaxis to decrease catheter-related, coagulase-negative staphylococcal sepsis, the Centers for Disease Control and Prevention discourage this practice.[21] An antibiotic lock regimen using 2 mg/mL had limited efficacy.[25] **Ventricular shunt infection:** *ISMP lists intraventricularly administered medications as high-alert and have an increased risk of causing significant patient harm if it is used in error*.[26] 60 mg/kg/day divided q 6 hr by IV administration. 5–20 mg/dose (50 mg/mL diluted with preservative-free NS to a final concentration of 1–5 mg/mL) directly into the ventricle (if the shunt is not externalized) or via the externalized shunt, which is then clamped for 1 hour after administration.[27–29]
Dosage adjustment in organ dysfunction	Adjust dosage in renal dysfunction.[30] If CrCl is 30–50 mL/min, give a normal dose q 12 hr; if CrCl is 10–29 mL/min, give normal dose q 18–24 hr; and if CrCl is <10 mL/min, adjust dosage based on serum concentrations.[30] Patients on extracorporeal membrane oxygenation have an increased circulating volume and transiently altered renal function; therefore, a suggested dose is 20 mg/kg q 24 hr.[31] Patients with malignancy may have increased clearance and require larger doses (i.e., mean dose of 71.5 mg/kg/day).[32,33] Although serum vancomycin concentration should not be routinely monitored, trough concentration may be helpful in patients who are not clinically responding.
Maximum dosage	Although higher doses have been used, 60 mg/kg/day, not to exceed the *adult* dose of 4g/day, is still recommended.[15]
Additives	None.
Suitable diluents	NS, LR, D5W, D5NS, D5LR.[2,34]
Maximum concentration	<5 mg/mL.[2,34] May use 10 mg/mL in fluid-restricted patients, but the risk of infusion reactions increase.[2]
Preparation and delivery	**Delivery system issues:** The potential for toxic effects from chemicals that may leach from the plastic containers into the single-dose, premixed IV preparation has not been determined.[35] Leaching has been reported to produce less than detectable concentrations for vancomycin PVC containers.[34] **Compatibility:** See Appendix D for PN compatibility information.[36]
IV push	Not recommended.[2]

Vancomycin HCl

Intermittent infusion	Over ≥60 minutes or ≤10 mg/min in *adults.*[2] (See Infusion-Related Cautions section; see Rare Adverse Effects in the Comments section.)
Continuous infusion	May be given by continuous IV infusion.[34] Vancomycin has a slow bactericidal activity and exhibits time-dependent killing. Some have proposed that administration by continuous infusion would maximize the time that vancomycin serum concentrations exceed the minimum inhibitory concentration (MIC) for the suspected organism and thereby enhance efficacy, prevent bacterial regrowth, and perhaps decrease toxicity.[37–39] Data for the administration of vancomycin by continuous infusion are extremely limited and have focused on *adults*[37,38,40–42] and neonates.[39,43] Neonates have received 10–40 mg/kg/day by continuous infusion.[39,43,44] A higher rate of nephrotoxicity occurred in *adult* patients receiving continuous infusions producing steady state concentrations ≥28 mg/mL.[42]
Other routes of administration	IM administration is not recommended because it may cause local tissue necrosis and has erratic absorption.[2,34] Has been given by inhalation[45,46] and intraventricular routes[27–29] for the treatment of methicillin-resistant *Staphylococcus aureus*. No information available to support administration by other routes. Chemical peritonitis (abdominal pain, fever, and changes in dialysate fluid) has been reported following IP delivery of vancomycin during continuous ambulatory peritoneal dialysis.[2] Discontinuation of IP vancomycin has shown to reverse the chemical peritonitis.
Comments	**Rare adverse effects:** Rapid IV administration may result in red man syndrome.[2] This syndrome may be accompanied by flushing and/or a maculopapular rash or erythematous rash on the face, neck, chest, and upper extremities. Symptoms usually begin minutes after start of the infusion. Symptoms usually resolve spontaneously after discontinuation of the infusion. Lengthen the infusion time to 2 hours and/or pretreatment with an antihistamine or H2 antagonist may prevent the syndrome.[47,48] Although extremely rare, nephrotoxicity may occur in patients with underlying kidney dysfunction, those receiving large doses, or in patients receiving concurrent nephrotoxic medications.[2] When vancomycin is discontinued, azotemia resolves in most patients.[2] Although most of these have occurred in patients who were given aminoglycosides concomitantly, the literature does not support the contention that the combination is more nephrotoxic in the pediatric population.[49–51] Vancomycin-associated hearing loss has been reported in patients with kidney dysfunction, preexisting hearing loss, and/or those receiving other ototoxic agents.[2] Vertigo, dizziness, and tinnitus have been reported rarely. An increased risk for hearing loss has been reported in neonates receiving vancomycin.[52] Hearing loss has been reported in *adults* receiving high doses.[53] DRESS syndrome has been reported.[54]
Comments	**Monitoring:** Studies have shown,[55,56] and the American Academy of Pediatrics[15] recommends, that routine monitoring of serum vancomycin concentrations is unnecessary. Although not validated in pediatric patients, an AUC/MIC ratio of >400 may be a better indicator of treatment success than trough concentrations.[17,57] Trough concentrations of 15–20 mcg/mL have recently been recommended for children with serious infections.[3] This higher concentration has also not been validated in the pediatric population. **Drug interactions:** Combination with other nephrotoxic or neurotoxic drugs requires close monitoring.[2] Consult appropriate resources for dosing recommendations before combining any drug with vancomycin. **Other:** Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable: (1) prosthetic cardiac valve or prosthetic material used for cardiac valve repair; (2) previous infective endocarditis; (3) congenital heart disease (CHD) in a person with a) unrepaired cyanotic CHD, including palliative shunts and conduits, b) completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure, c) repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization); and (4) cardiac transplantation recipients who develop cardiac valvulopathy.[18]

Vasopressin

Brand names	Pitressin, argipressin, generic
Medication error potential	Look-alike, sound-alike drug names. USP reports that vasopressin has been confused with desmopressin and oxytocin. Pitressin has been confused with pitocin.[1]
Contraindications and warnings	**Contraindications:** Anaphylaxis or hypersensitivity to vasopressin or any of its components.[2] **Warnings:** Use in patients with vascular disease, especially of the coronary arteries, may precipitate angina pain or myocardial infarction and should only be used with extreme caution.[2] Water intoxication may occur; monitor for early signs including drowsiness, listlessness, and headache to prevent resultant seizures and coma.[2]
Infusion-related cautions	Extravasation of IV infusion may result in tissue necrosis.[3] (See Appendix E for extravasation treatment.)
Dosage	*Note that dosing UNITS are often different among indications (e.g., units/kg/hr versus units/kg/min) and may or may not be based on patient weight.* **Diabetes insipidus** **Continuous IV infusion:** Initially 0.0005 unit/kg/hr (0.5 milliunits/kg/hr) doubling the dose q 30 min until urine osmolality is twice that of plasma osmolality and urine output is $<$2 mL/kg/hr.[4] The dosage required rarely exceeds 0.01 unit/kg/hr (10 milliunits/kg/hr).[4] A 3-day-old baby and a 3-year-old child were started on 0.003 unit/kg/hr (3 milliunits/kg/hr). Polyuria resolved and the drug was weaned over several days.[5] **IM or SC injection:** In *adults*, 5–10 units BID to TID as needed. The manufacturer recommends that doses for pediatric patients be proportionately reduced.[6] **Shock** **Catecholamine-refractory shock:** A case series of three patients from 3 months to 13 years of age reported initial doses of 0.0002–0.0005 units/kg/min (0.2–0.5 milliunits/kg/min) titrated up to 0.0005–0.002 units/kg/min (0.5–2 milliunits/kg/min). In all three patients, concomitant catecholamines were able to be weaned to off within 12 hours.[7] **Vasodilatory shock:** Two retrospective reports of five and 11 patients described the ability to wean other pressors after initiating vasopressin at doses of 0.0003–0.004 units/kg/min (0.3–4 milliunits/kg/min) titrated up to 0.001–0.008 units/kg/min (1–8 milliunits/kg/min).[8,9] One patient (14 years old) received 0.04–0.06 units/min.[8] A randomized, double-blind, placebo-controlled trial in 69 pediatric patients with vasodilatory shock received a median 0.0011 units/kg/min (1.1 milliunits/kg/min) with interquartile range 0.0007–0.0018 units/kg/min (0.7–1.8 milliunits/kg/min). This study found no differences (for vasopressin versus placebo) in time to achieve hemodynamic stability, vasoactive-free days, organ failure-free days, ventilator-free days, or ICU duration. Additionally, mortality was 30% in the vasopressin group compared to 15.6% placebo ($P > .05$).[10] In *adults* with septic shock, continuous low-dose infusion of 0.01–0.04 unit/min in conjunction with other pressors is supported.[11,12] However, the VASST trial, a multicenter, randomized, double-bind trial comparing vasopressin 0.01–0.03 unit/min to norepinephrine for patients with septic shock already receiving norepinephrine, found that vasopressin did not reduce 28-day mortality (the primary endpoint).[13]

Dosage *(cont.)*

Gastrointestinal (GI) bleeding (other therapies have decreased the use of vasopressin for this indication)

Age-based[14]

0.1 unit/min as a continuous infusion; increased by 0.05 unit/min each hour up to a maximum of

<5 years: 0.2 unit/min.

5–12 years: 0.3 unit/min.

>12 years: 0.4 unit/min.

Weight-based

An initial infusion of 0.3 unit/kg (up to 20 units) infused over 20 minutes may be used prior to a continuous infusion of 0.2–0.4 unit/1.73 m^2/min. The infusion is maintained for 12 hours after bleeding stops and then tapered to off over the next 24–36 hours.[15]

0.002–0.005 unit/kg/min up to a maximum of 0.01 unit/kg/min was studied in 17 children (mean age 7.2 years).[16] Doses higher than 0.01 unit/kg/min were no more efficacious at controlling bleeding but resulted in significantly more complications (electrolyte disturbances, fluid overload, hypertension, cardiac dysrhythmias).

Cardiac arrest: 0.4–1 unit/kg bolus (maximum 40 units/dose),[3] although the Pediatric Advanced Life Support (PALS) authors found insufficient evidence to recommend for or against the use of vasopressin.[17] A four-patient case series found evidence that vasopressin administration may be beneficial during prolonged pediatric cardiac arrest.[18] Results from the American Heart Association National Registry of Cardiopulmonary Resuscitation demonstrate an association with vasopressin use and worse return of a sustained circulation for pediatric in-hospital cardiac arrest; however, several limitations of the registry have been identified allowing for a potential patient selection bias.[19]

Dosage adjustment in organ dysfunction

No dosage adjustment required in renal dysfunction; titrate to effect.[20] Patients with cirrhosis may require lower doses.[21]

Maximum dosage

Diabetes insipidus (IV): 0.01 unit/kg/hr (10 milliunits/kg/hr).[4]

GI bleeding: ≥0.01 unit/kg/min has been used but resulted in significantly more adverse effects.[16]

Additives

Contains chlorobutanol as a preservative.[2,6] May also contain sodium chloride.[2]

Suitable diluents

D5W, NS.[22]

Maximum concentration

1 unit/mL.[22]

Preparation and delivery

Undiluted for SC or IM use.[2,22]

0.1–1 unit/mL for continuous IV infusion.[22]

IV push

20 units/mL.[3]

Vasopressin

Intermittent infusion	Not indicated.
Continuous infusion	0.1–1 unit/mL.[22]
Other routes of administration	IM or SC.[2,22] IO (preferred) and ET administration may be used during CPR if unable to obtain IV access.[17,21] Intra-arterial infusion may be used for GI hemorrhage.[21,22]
Comments	**Monitoring:** ECG, blood pressure,[3] and fluid and electrolyte status should be monitored.[2,23] **Drug interactions:** The antidiuretic effects of vasopressin may be potentiated when used with carbamazepine, chlorpropamide, clofibrate, urea, fludrocortisone, and tricyclic antidepressants. Conversely, concomitant use of demeclocycline, norepinephrine, lithium, and heparin may antagonize the effects of vasopressin.[2]

Vecuronium Bromide

Brand names	Norcuron, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. USP reports that vecuronium has been confused with pancuronium and rocuronium; no patient harm resulted. USP reports that vecuronium has been confused with vancomycin; patient harm resulted. USP also reports that vecuronium has been confused with Zemuron; patient death resulted.[2] ISMP and USP report that Norcuron has been confused with Narcan; no patient harm resulted.[2,3] USP also reports that Norcuron has been confused with Natrecor; patient death resulted.[2]
Contraindications and warnings	**U.S. boxed warning:** Vecuronium should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.[4] **Contraindications:** Hypersensitivity to vecuronium or any of its components.[4] **Other warnings:** Use carefully under the supervision of experienced clinicians; personnel should be skilled in airway management, resuscitation, and respiratory support. Intubation and ventilatory support equipment, including oxygen therapy, should be readily available. Reversal agents should be readily available when giving vecuronium.[4]
Infusion-related cautions	Flushing, erythema, pruritus, urticaria, bronchospasm, and hypotension are uncommon but may occur.[4,5] In one study, 69% of patients with confirmed rocuronium allergy demonstrated cross-sensitivity to vecuronium.[6]
Dosage	*Respiratory function must be supported during use of this agent. Concurrent administration of a sedative is also necessary. Monitoring of neuromuscular transmission with a peripheral nerve stimulator is recommended during continuous infusion or with repeated dosing.*[4,7] Because vecuronium does not cause histamine release, it is considered the neuromuscular blocking agent of choice in patients with allergies and/or asthma.[8,9] Dosing adjustment for hypothermia: During moderate-to-deep hypothermia during cardiopulmonary bypass (lowest nasopharyngeal temperature range 17°C to 29°C), vecuronium infusion requirements decreased by 84% to 92% in order to maintain a constant level of blockade.[10] **Dosing adjustment for obesity:** Doses should be based on ideal body weight.[11] **Induction and maintenance of neuromuscular blockade** **Neonates:** 0.1 mg/kg for nonemergent intubation.[12] (See Other in the Comments section.) Initial dose 0.02–0.1 mg/kg[13,14]; may be repeated as needed to maintain desired neuromuscular blockade. Maintenance doses during general anesthesia may need to be reduced to 0.01–0.015 mg/kg.[4] Continuous infusions of 0.07–0.18 mg/kg/hr (1.2–3 mcg/kg/min) have been reported.[14] **Infants, children, and adolescents:** Initial dose 0.05–0.1 mg/kg[4,8,13–17]; American Academy of Pediatrics (AAP) recommends 0.2 mg/kg for intubation.[18] Doses may be repeated as needed to maintain desired neuromuscular blockade. Maintenance doses during general anesthesia may need to be reduced to 0.01–0.015 mg/kg.[4] Continuous infusions range from 0.05–0.15 mg/kg/hr (0.8–2.5 mcg/kg/min).[4,8,14,15,17]

Vecuronium Bromide

Dosage adjustment in organ dysfunction	To avoid prolonged neuromuscular blockade, give smaller initial doses to anephric patients. Patients with cirrhosis and cholestasis may experience prolonged recovery times.[4]
Maximum dosage	A single dose of 0.4 mg/kg has been used safely in children 2–9 years old with normal renal and hepatic function.[16] The largest reported continuous infusion rate was 0.27 mg/kg/hr (4.5 mcg/kg/min) for 21 hours.[14]
Additives	If bacteriostatic water for injection is used to reconstitute vecuronium, the resulting solution will contain benzyl alcohol.[4,19] (See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.)
Suitable diluents	D5W, D5NS, NS, LR.[4,19]
Maximum concentration	1 mg/mL.[4,19]
Preparation and delivery	In neonates, use SW for reconstitution to avoid the administration of benzyl alcohol.[19] Vecuronium should not be mixed or administered with alkaline solutions.[4] For PN compatibility information, please see Appendix D.
IV push	1 mg/mL administered rapidly over seconds.[4,19]
Intermittent infusion	Not generally recommended.[4] An intermittent regimen (0.1 mg/kg q 1 hr) was compared to a continuous infusion regimen (bolus of 0.15 mg/kg followed by 0.06 mg/kg/hr [1 mcg/kg/min]) in 12 patients ages 3 weeks to 13.5 years. The continuous infusion regimen resulted in significantly less cumulative vecuronium administration.[15]
Continuous infusion	0.1–0.2 mg/mL preferred.[4,14,17,19] In fluid-restricted patients, 0.4 mg/mL was used in one study.[14] Another reference states that up to 1 mg/mL may be given via continuous infusion.[20]
Other routes of administration	Should not be given IM.[4,19] No information available to support administration by other routes.
Comments	**Significant adverse effects:** Prolonged paralysis has been reported in several patients after long-term infusion of vecuronium.[21–23] Acute quadriplegic myopathy resulted when a 17-month-old infant was intubated for 24 days and treated with vecuronium and high-dose methylprednisolone.[24] Sinus node exit block occurred in a 14-year-old after administration of 0.08 mg/kg.[25] **Drug interactions:** Concomitant administration of corticosteroids[26–28] and certain antibiotics (e.g., aminoglycosides and polymyxin B)[29,30] with neuromuscular blockers has been shown to be a risk factor for prolonged paralysis. Reduce vecuronium dose to 0.04–0.06 mg/kg in patients receiving succinylcholine, enflurane, or isoflurane.[4] Concomitant use with atracurium in an equipotent dose is more potent than either agent alone.[31]

Vecuronium Bromide

Comments *(cont.)*

Other: Disruption of the blood brain barrier in critical illness may cause penetration of vecuronium or atracurium into the CNS, resulting in dilated, nonreactive pupils. Three such cases were reported in a pediatric oncology unit.[32]

For neonatal nonemergent intubations, AAP recommends that vagolytic and muscle relaxant agents should be considered, and that analgesic agents or anesthetic doses of a hypnotic agent should be administered. Rocuronium or vecuronium is preferred over other available neuromuscular blocking agents.[12]

Verapamil HCl

Brand names	Generic
Medication error potential	High-alert medication associated with an increased risk of significant patient harm should an error occur.[1]
Contraindications and warnings	**Contraindications[2]:** Severe hypotension or cardiogenic shock, second- or third-degree atrioventricular (AV) block (unless patient has a pacemaker), sick sinus syndrome (unless patient has a pacemaker), severe coronary heart failure, treatment with beta blockers (should be administered hours apart), atrial flutter or atrial fibrillation with an accessory bypass tract (Wolff-Parkinson-White syndrome,[3,4] ventricular tachycardia, and known hypersensitivity to verapamil. The initial use should be in facilities with appropriate monitoring and resuscitation facilities including direct-current cardioversion availability.[2 5,6] Continuous ECG monitoring should be performed during infusion.[5,6]
Infusion-related cautions	Hypotension, bradycardia, tachycardia, asystole, and arrhythmias may occur, particularly in patients with sinus node dysfunction or impaired AV conduction.[7] Calcium chloride 10 mg/kg should be at the bedside in the event of hypotension.[5]
Dosage	PALS guidelines state that verapamil should not be used in infants during CPR because it may cause refractory hypotension and cardiac arrest.[7] Verapamil is not included in the *2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care*.[8] **Tachyarrhythmias** **Neonates and infants:** While verapamil has been used in this age group, severe hemodynamic side effects including death have been reported[9–12]; hence, it should not be used unless an ICU physician or cardiologist is present and continuous ECG monitoring is used. Doses of 0.1–0.2 mg/kg (usually 0.75–2 mg).[2,5,13–17] If necessary, the dose can be repeated 30 minutes after the initial dose.[5,15] **Children 1–15 years:** Initially, 0.1–0.3 mg/kg[2,6,13–16,18] (usually 2–5 mg; maximum 5 mg).[2] If necessary, the dose (≤10 mg) can be repeated one time 30 minutes after the initial dose.[2]
Dosage adjustment in organ dysfunction	Use with caution and monitor ECG (for PR prolongation) and blood pressure for signs of toxicity in patients with renal insufficiency.[5] The dose should be decreased by 50% in *adults* with cirrhosis.[19]
Maximum dosage	**Neonates and infants:** 0.2 mg/kg and ≤2 mg/dose.[2] **1–15 years:** 0.3 mg/kg and ≤10 mg/dose.[2] An 18-year-old with anticholinergic-induced torsades de pointes and prolonged QT interval unresponsive to standard therapies was successfully treated with 3 doses of 5 mg (0.1 mg/kg) verapamil followed by an infusion of 5 mcg/kg/min.[20]
Additives	Contains 8.5 mg sodium chloride/mL.[2,21]
Suitable diluents	D5W, D5½NS, D5NS, D5LR, D5R, ½NS, NS, LR, R.[21]

Verapamil HCl

Maximum concentration	2.5 mg/mL (undiluted).[2]
Preparation and delivery	**Stability:** Store at room temperature (i.e., 15°C to 30°C). May precipitate in solutions having a pH ≥6. Use only clear solutions.[2] **Photosensitivity:** Protect from light during storage.[2]
IV push	Over ≥2–3 minutes.[2,21] May prolong infusion time (4 minutes) if the patient's is borderline is hypotensive.
Intermittent infusion	Not indicated.
Continuous infusion	Has been used in *adults*.[22–24]
Other routes of administration	Not indicated.
Comments	**Adverse effects:** Apnea, cardiovascular collapse, and respiratory arrest have been reported in pediatric patients, particularly those <1 year of age.[9–12] Verapamil should be used cautiously if a patient receiving other medications known to block the SA/AV node (e.g., digoxin) or reduce sympathetic outflow (e.g., clonidine) as profound bradycardia can occur.[5] Brief myoclonic seizures developed in an 18-month-old patient following IV verapamil.[25] A 15-year-old with Duchenne muscular dystrophy was given 7 doses of 5 mg verapamil over 20 hours and had resolution of the tachyarrhythmia.[26] However, 4 hours after the last dose, severe bradycardia and hypotension occurred, and the child died. The death was not attributed to verapamil because of the length of time since the last dose and the short half-life of verapamil. A 17-year-old with Duchenne muscular dystrophy developed irreversible respiratory failure felt to be related to verapamil.[27] **Drug interactions:** Verapamil is a substrate for CYP3A4 and moderately inhibits CPY3A4 and, thus, is subject to a number of drug interactions. Appropriate references should be consulted prior to combining any drug with verapamil.

VinBLAStine Sulfate

Brand names	Velban, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP and USP report that vinBLAStine has been confused with vinCRIStine; no patient harm resulted.[2,3]
Contraindications and warnings	**U.S. boxed warning:** Should only be administered by individuals with experience in the administration of vinBLAStine. VinBLAStine may cause extravasation. (See Infusion-Related Cautions section.) VinBLAStine is fatal if given intrathecally.[4] **Contraindications:** VinBLAStine should not be administered to patients with significant granulocytopenia or in the presence of a bacterial infection.[4] (See Significant Adverse Effects in the Comments section.) **Other warnings:** May cause serious stomatitis, neurological toxicity, leukopenia, and dyspnea.[4] (See Significant Adverse Effects in the Comments section.)
Infusion-related cautions	VinBLAStine is only administered IV. IT administration of vinBLAStine is fatal.[4,5] Extravasation of vinBLAStine can cause considerable local tissue irritation.[4,6] The infusion should be stopped if the patient complains of discomfort. Because of extravasation and infiltration risk, small veins in the dorsum of the hand or foot and scalp veins should be avoided if at all possible. Local injection of hyaluronidase and application of moderate heat to the area may lessen pain and potential damage.[4] (See Appendix E for additional information regarding extravasation treatment.)
Dosage	Consult institutional protocol for complete dosing information. VinBLAStine is used alone and in combination with a variety of antineoplastic agents for the treatment of Hodgkin lymphoma, non-Hodgkin lymphoma, histiocytic lymphoma, testicular cancer, Kaposi sarcoma, histiocytosis X, and others. While it can be used as monotherapy, it is often part of a multidrug regimen, and the timing of doses for all drugs is critical to achieve the optimal outcome. VinBLAStine is usually dosed once a week and only after the WBC count is $<4000/m^3$; however, there are specific protocols that vary. Some regimens that have been used in children are listed below: **Histiocytosis X:** 6.5 mg/m^2 weekly for 24 weeks as a single agent or with prednisone.[7] **Hodgkin disease (combined with other agents):** 6 mg/m^2 q 7 days for up to 6 weeks.[8, 9] **Testicular cancer (combined with other agents):** 3 mg/m^2 on two separate days[10] or on protocol days 22 and 23 or days 1 and 2.[11] In *adults*, the initial dose is usually 3.7 mg/m^2 and this is increased by 1.8 mg/m^2 weekly until the WBC count is $3000/m^2$ or a maximum dose of 18.5 mg/m^2 is reached. Once the dose that suppresses the WBC count to $<3000/m^2$ is reached, the maintenance dose should be decreased by one step (1.8 mg/m^2). Usual weekly range of doses in *adults* is 5.5–7.4 mg/m^2.[12]
Dosage adjustment in organ dysfunction	No dose reduction is needed in patients with renal dysfunction.[13] VinBLAStine doses should be reduced in patients with hepatic insufficiency.[14] The manufacturer recommends a 50% dose reduction in patients with a direct serum bilirubin >3 mg/dL.[4]

VinBLAStine Sulfate

Maximum dosage	Maximum weekly dose should not exceed 18.5 mg/m^2 in *adults*.[4] Refer to treatment protocols for maximum-dose guidelines.
Additives	May contain benzyl alcohol 0.9%.[5] (See Preparation and Delivery section. See Appendix C for more specific information about potential adverse effects and/or benzyl alcohol toxicity in neonates.)
Suitable diluents	D5W, LR, NS.[4,5]
Maximum concentration	1 mg/mL.[4,5]
Preparation and delivery	Reconstitute with NS or bacteriostatic NS (with benzyl alcohol). Also available as a solution of 1 mg/mL (preserved with benzyl alcohol).[5] **Preparation:** VinBLAStine must be dispensed with a sticker affixed directly to the container that states "Fatal if given intrathecally. For IV use only."[4,5] VinBLAStine must also be dispensed in overwrap, which bears the statement "Do not remove covering until the moment of injection. Fatal if given intrathecally. For IV use only."[4,5]
IV push	1 mg/mL administered via an intact, free-flowing IV needle or catheter over 1 minute.[5]
Intermittent infusion	Although vinBLAStine has been administered by this method, it is not recommended because of the risk of infiltration.[5]
Continuous infusion	Not recommended.[5]
Other routes of administration	Contraindicated.[4,5]
Comments	**Significant adverse effects:** VinBLAStine is associated with severe hematologic effects, primarily leukopenia (granulocytopenia), and rarely anemia and thrombocytopenia. The hematologic effects appear to be dose-related. VinBLAStine should not be given if the WBC count is $<$4000/m^3.[4] Neurotoxicity has been observed following vinBLAStine administration, but this adverse effect is much less common than with vinCRIStine.[15] Dyspnea has not been observed with vinBLAStine alone,[16] but there have been numerous case reports of an acute, temporally related, respiratory distress syndrome that occurs within 1–5 hours following the combination of vinBLAStine and mitomycin C. Some of these acute reactions have been fatal.[16–22] The incidence of this toxic pulmonary reaction has been estimated to be as high as 3% to 6%.[17] VinBLAStine is associated with a minimal ($<$10%) risk of emesis.[23,24] Generally, prophylaxis for acute and delayed emesis is not needed. Patients may receive one-time prophylaxis with an antiemetic medication. Breakthrough medications may be offered. Selection should be based on what the patient is currently receiving for acute antiemesis prophylaxis. **Monitoring:** CBC with differential, serum uric acid, and hepatic function.[4,5] **Drug interactions:** VinBLAStine is major substrate for CYP3A4 and a minor substrate for CYP2D6; there is a potential for drug interactions.[4,5] Consult appropriate resources for dosing recommendations before combining any drug with vinBLAStine.

VinCRIStine Sulfate

Brand names	Vincasar PFS, Oncovin, generic
Medication error potential	ISMP high-alert medication that has an increased risk of causing significant patient harm if it is used in error.[1] Look-alike, sound-alike drug names. ISMP and USP report that vinCRIStine has been confused with vinBLAStine; no patient harm resulted.[2,3] USP also reports that vinCRIStine has been confused with vinorelbine; no patient harm resulted.[3]
Contraindications and warnings	**U.S. boxed warning:** Should only be administered by individuals with experience in the administration of vinCRIStine. VinCRIStine may cause extravasation. (See Infusion-Related Cautions section.) VinCRIStine is fatal if given intrathecally.[4] **Contraindications:** VinCRIStine should not be administered to patients with demyelinating forms of Charcot-Marie-Tooth syndrome.[4] **Other warnings:** VinCRIStine has been associated with serious constipation, neurotoxicity, respiratory effects, and urinary tract disturbances.[4] (See Significant Adverse Effects in the Comments section.)
Infusion-related cautions	VinCRIStine is only administered IV.[4,5] IT administration of vinCRIStine is fatal.[4–7] Because extravasation may cause tissue sloughing and necrosis, the infusion should be stopped if the patient complains of discomfort.[8,9] Because of extravasation and infiltration risk, small veins in the dorsum of the hand or foot and scalp veins should be avoided if at all possible. Local injection of hyaluronidase and application of moderate heat to the area may lessen pain and potential damage.[4]
Dosage	Please consult institutional protocol for complete dosing information. VinCRIStine is used as a component of combination therapy to treat childhood acute lymphocytic (lymphoblastic) leukemia, Hodgkin disease, non-Hodgkin lymphoma, neuroblastoma, rhabdomyosarcoma, Wilms Tumor, Kaposi sarcoma, brain tumors, small cell lung cancer, and other neoplastic diseases. One protocol for high-risk acute lymphoblastic leukemia included vinCRIStine on induction days 8, 15, 22, and 29; during block 1 of therapy on days 1 and 8; and as part of reinduction on days 8, 15, 22, and 29.[10] A protocol for treating Hodgkin disease included doses of vinCRIStine on day 0 (with the complete schedule of chemotherapies repeated q 28 days) or on day 42 of a 63-day multiple chemotherapy regimen.[11] **Usual doses given no more frequently than weekly[8,12,13]:** **<10 kg or body surface area (BSA) <1 m^2:** 0.05 mg/kg (up to 2 mg). **≥10 kg:** 1–2 mg/m^2 (up to 2 mg). ***Adults*:** 0.4–1.4 mg/m^2 (up to 2 mg). In infants, vinCRIStine clearance is more closely related to body weight than BSA.[14] **Neuroblastoma:** 1 mg/m^2 as an IV continuous infusion (with doxorubicin) for 72 hours.[8]
Dosage adjustment in organ dysfunction	Dose should be reduced in patients with hepatic insufficiency.[15] A 50% reduction in dose is recommended if direct serum bilirubin is >3 mg/dL.[4,8] No dose reduction is needed in patients with renal dysfunction.[16]

Maximum dosage	Most, but not all, clinical trials and treatment protocols have maximum-dose guidelines of 2 mg in order to minimize neurotoxicity.[12,13,17] However, some clinicians have questioned the appropriateness of the 2-mg maximum vinCRIStine dose.[18] Refer to treatment protocols for maximum-dose guidelines. In pediatric patients less than 13 years of age, severe toxicity symptoms may occur after doses of 3–4 mg/m^2 and death has occurred following doses 10 times the recommended therapy.[4]
Additives	None.
Suitable diluents	D5W, NS.[4,5]
Maximum concentration	1 mg/mL.[5]
Preparation and delivery	VinCRIStine must be dispensed with a sticker affixed directly to the container which states "Fatal if given intrathecally. For IV use only." VinCRIStine must also be dispensed in overwrap that bears the statement "Do not remove covering until the moment of injection. Fatal if given intrathecally. For IV use only."[4,5]
IV push	1 mg/mL administered via an intact, free-flowing IV needle or catheter over 1 minute.[5]
Intermittent infusion	May dilute with suitable diluent and infuse over 4–8 hours.[5]
Continuous infusion	May dilute with suitable diluent and infuse continuously.[5]
Other routes of administration	Not recommended; for IV infusion only.[4,5]
Comments	**Significant adverse effects:** The dose-limiting effect of vinCRIStine is neurotoxicity.[4,8] Severe vinCRIStine-associated neurotoxicity has been observed with concurrent administration of drugs that inhibit hepatic cytochrome P450 isoenzymes.[19] (See Drug Interactions below.) Hepatic veno-occlusive disease has been reported in pediatric patients receiving vinCRIStine as part of standard combination chemotherapy regimens. Some of these patients had fatal outcomes.[4] Intestinal pseudo-obstruction has been reported in children receiving vinCRIStine and may be reversible with reduced doses, dose interruptions, and symptom management.[20] VinCRIStine is associated with a minimal (<10%) risk of emesis.[21,22] Generally, prophylaxis for acute and delayed emesis is not needed. Patients may receive one time prophylaxis with an antiemetic medication. Breakthrough medications should be offered. Selection should be based on what the patient is currently receiving for acute antiemetic prophylaxis. **Monitoring:** CBC with differential, uric acid levels, serum electrolytes, hepatic function, and neurologic examination.[4,8] **Drug interactions:** VinCRIStine is a major substrate for CYP3A4. Concomitant use with drugs that inhibit the CYP3A4 isoenzyme (e.g., azole antifungals, cyclosporine, and macrolide antibiotics) may result in severe neurotoxicity.[19] Consult appropriate resources for dosing recommendations before combining any drug with vinCRIStine.

VinCRIStine Sulfate

Comments *(cont.)*

Other: VinCRIStine should not be given to patients receiving radiation through ports that include the liver due to risk of potentially fatal hepatitis.[23]

In overdose, treatment includes fluid restriction due to likelihood of SIADH (syndrome of inappropriate antidiuretic hormone), prophylactic phenobarbital, enemas to prevent ileus, daily hemoglobin and hematocrit to evaluate need for transfusion, and monitoring the cardiovascular system. Some have suggested that leucovorin calcium 100 mg IV q 3 hr for 24 hours and then q 6 hr for at least 48 hours may be of value.[4,8]

Vitamin A

Brand names	Aquasol A Parenteral (water-miscible vitamin A palmitate)
Medication error potential	Look-alike, sound-alike drug names. USP reports that Aquasol A has been confused with Aquasol E.[1]
Contraindications and warnings	**Contraindications:** Hypervitaminosis A, or hypersensitivity to any product components.[2]
Infusion-related cautions	Not intended for IV use.[2]
Dosage	**Vitamin A deficiency**[2] **Infants:** 7500–15,000 units/day IM for 10 days. **1–8 years of age:** 17,500–35,000 units/day IM for 10 days. ***Adults*:** 100,000 units/day IM for 3 days followed by 50,000 units/day IM for 2 weeks. **Decrease morbidity from bronchopulmonary dysplasia/chronic lung disease in preterm infants:** 2000 units (n = 20) or placebo (n = 20) IM was given to very low birth weight (VLBW; 700–1300 g) neonates with increased risk for bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) on day 4 of life and then every other day for 28 days. Vitamin A status was improved and morbidity associated with BPD/CLD was decreased.[3] In a larger, multicenter study, either 5000 units (n = 405) or placebo (n = 402) was given IM 3 times weekly for 4 weeks in extremely low birth weight (ELBW; 401–1000 g) infants beginning on day of life 1–4. Compared to controls, the treated infants had improved vitamin A serum concentrations, and the combined incidence of death or CLD at 36 weeks postmenstrual age was decreased in treated infants versus controls (55% versus 62%, respectively).[4] A follow-up study evaluating the long-term outcome when these infants were 18–22 months adjusted age found no differences in neurodevelopmental outcomes or pulmonary morbidity between the vitamin A group and controls.[5] One group recommended the following regimen for VLBW infants at high risk of BPD/CLD[6]: 2000 units/kg/dose IM on day of life 1 and every other day until enteral feedings account for 75% of total energy intake, at which time the route is changed to enteral and the dose increased to 4000 units/kg/dose given until discharge from the neonatal ICU. Should the patient be placed NPO, the IM dose and route are resumed. Vitamin A and retinol binding protein concentrations should be measured weekly. (See Comments section.)
Dosage adjustment in organ dysfunction	Elevated serum retinol concentrations accompanied by clinical toxicity were reported in one *adult* and two children with renal failure receiving PN containing standard multivitamins.[7]
Maximum dosage	35,000 units in children[2]; 5000 units in neonates.[4]
Additives	Contains 12% polysorbate 80 and 0.5% chlorobutanol.[2] (See Appendix C for specific information about potential polysorbate adverse effects.)
Suitable diluents	Not applicable.
Maximum concentration	50,000 USP units (15 mg retinol)/mL (undiluted).[2]

Vitamin A

Preparation and delivery	**Photosensitivity:** Protect from light.[2]
IV push	Not for IV use.[2]
Intermittent infusion	Not for IV use.[2]
Continuous infusion	Not for IV use.[2]
Other routes of administration	For IM administration only.[2]
Comments	**Monitoring:** The target serum concentrations are vitamin A 30–60 mcg/dL and retinol binding protein >2.5 mg/dL. Vitamin A concentrations >100 mcg/dL are potentially toxic.[6] In particular, measuring serum concentrations is recommended in patients receiving glucocorticoids because steroids increase plasma concentrations of vitamin A.[8] This confounds the assessment of adequacy of vitamin A intake. Some authors suggest withholding vitamin A supplementation during dexamethasone therapy.[6]

Vitamin K_1–Phytonadione

Brand names	AquaMEPHYTON; various manufacturers
Medication error potential	Look-alike, sound-alike drug names. USP reports that vitamin K has been confused with Urocit-K and that phytonadione has been confused with Coumadin and phenytoin sodium.[1]
Contraindications and warnings	**U.S. boxed warning:** Severe reactions including fatalities with IV administration even when the product is diluted and infusion has been slow. Severe reactions have also been noted following IM administration. Usually these resemble anaphylaxis or hypersensitivity type reactions. Restrict IV and IM use to situations when the SC route is not feasible.[2] **Contraindications:** Hypersensitivity to phytonadione or any of its components.[2]
Infusion-related cautions	See U.S. Boxed Warning in the Contraindications and Warnings section.[2]
Dosage	**Neonatal hemorrhagic disease** **Prophylaxis:** Usually given within 1 hour of birth.[2,3] **≤1500 g:** 0.5 mg IM.[2–6] **>1500 g:** 1 mg IM.[2–6] **Treatment:** Usually 1 mg; however, larger doses may be needed if the mother was receiving anticoagulant therapy.[2,4,7–10] **Prothrombin deficiency (malabsorption syndromes, broad spectrum antibiotics, etc.)** **Older children and adolescents:** 2 mg.[11,12] **Reversal of over-warfarinization in children:** 30 mcg/kg IV (0.35–1 mg) was used in seven children (age not reported).[13,14]
Dosage adjustment in organ dysfunction	None noted. Those with liver dysfunction may require larger than usual doses[2] or more than 1 dose.
Maximum dosage	5 mg in children.[13] In *adults* with anticoagulant-induced hypoprothrombinemia, doses are usually 2.5–10 mg; however, doses up to 50 mg may be needed.[2] It is prudent to limit the dose to the lowest effective amount so the patient can resume anticoagulation at the appropriate level.[15] Failure to respond may indicate that the underlying disease may be unresponsive to vitamin K.
Additives	Contains benzyl alcohol and aluminum.[2,16] (See Appendix C for specific information about potential benzyl alcohol toxicity.) Premature neonates may be at particular risk for aluminum toxicity.[2]
Suitable diluents	D5W, NS, D5NS.[2,16]
Maximum concentration	10 mg/mL (undiluted).[2]

Vitamin K_1–Phytonadione

Preparation and delivery	**Compatibility:** See Appendix D for PN compatibility information. **Photosensitivity:** Protect from light during storage.[2]
IV push	IV push rate should not exceed 1 mg/min.[2,16] IV administration should be restricted due to the potential for severe adverse reactions.[2]
Intermittent infusion	Over 15–30 minutes.[13]
Continuous infusion	Specified dose can be added to PN solutions.[16,17]
Other routes of administration	The preferred route of administration is SC,[2] while the IM route should be restricted to occasions where the SC route cannot be used.[2]
Comments	**Monitoring:** Improvement in hemostasis may not be detectable until 1–2 hours after administration.[2,13] Some recommend measurement of international normalized ratio 4–6 hours after the dose in those at high risk of bleeding or 12 hours after the dose in less severe cases of over-warfarinization.[13] Hyperbilirubinemia and severe hemolytic anemia have occurred in neonates receiving larger doses.[2] Two neonates who received IV phytonadione for prophylaxis developed late-onset hemorrhagic disease.[18]

Voriconazole

Brand names	Vfend
Medication error potential	Look-alike, sound-alike drug names. USP reports that Vfend has been confused with Venofer.[1]
Contraindications and warnings	**Contraindications:** Concomitant administration with astemizole, cisapride, pimozide, quinidine, or terfenadine is contraindicated due to the increased risk of QT prolongation and torsades de pointes. Also contraindicated with concomitant use of sirolimus, rifampin, carbamazepine, long-acting barbiturates, high-dose ritonavir, rifabutin, ergot alkaloids, and St. John's Wort.[2] (See Drug Interactions in the Comments section.) Voriconazole is contraindicated in patients with a hypersensitivity to the drug or any of its components.[2] **Warnings:** Visual adverse effects are commonly reported with voriconazole therapy.[2] The effect of voriconazole on visual function is not known if therapy is prolonged beyond 28 days.[2] Visual function should be monitored in patients receiving voriconazole beyond 28 days.[2] Prolonged therapy should be used with caution in infants and children who are unable to vocalize visual effects.[2] Voriconazole has been associated with uncommon cases of hepatotoxicity, including liver failure and death. Liver function should be monitored before and during therapy. Cessation of therapy should be considered in patients with clinical signs and symptoms of liver disease.[2] Contains hydroxypropyl-beta-cyclodextrin.[2] (See Dosage Adjustment in Organ Dysfunction and Additives sections.)
Infusion-related cautions	Anaphylactic-type reactions, typically presenting upon initiation of the infusion, have occurred uncommonly.[2]
Dosage	The most commonly reported dosage regimen in pediatric patients is a loading dose of 6 mg/kg q 12 hr for 2 doses followed by a maintenance dose of 4 mg/kg q 12 hr.[3,4] Other published doses are summarized below: **Neonates and infants:** Experience with voriconazole in neonates and infants is limited.[5] One report of two cases of extremely low birth weight (ELBW) infants receiving 3 mg/kg IV q 12 hr for 2 doses, then 2 mg/kg IV q 12 hr documented serum concentrations below that seen in *adults*; therapy was successful in both infants.[6] Another report in an ELBW infant used 4 mg/kg q 12 hr also with concentrations below those found in *adults.*[7] Two reports in infants (one preterm) utilized initial dosing of 6 mg/kg IV q 12 hr.[8,9] The dose in the preterm infant was increased to 6 mg/kg IV q 8 hr to obtain serum concentrations similar to that seen in *adults*.[8] A 3-month-old received 6 mg/kg IV q 12 hr for 2 doses, then 4 mg/kg IV q 12 hr.[10] One reference suggests a dosing regimen of 8 mg/kg IV q 12 hr for 2 doses, then 6 mg/kg IV q 12 hr.[11] **Children[2–5,11–16]** **Loading dose:** 6–8 mg/kg IV q 12 hr for 2 doses. **Maintenance dose:** 4–10 mg/kg IV q 12 hr. Children have required larger doses than *adults* to maintain similar concentrations.[4,14,15]
Dosage adjustment in organ dysfunction	**Hepatic impairment:** Patients with mild-to-moderate hepatic cirrhosis (Child-Pugh Class A or B) should receive a standard loading dose and 50% of maintenance dose.[2] Dosing has not been evaluated in patients with severe hepatic cirrhosis (Child-Pugh Class C) or chronic hepatitis B or C.[2]

Dosage adjustment in organ dysfunction *(cont.)*	**Renal impairment:** Oral voriconazole is preferred in patients with CrCl <50 mL/min due to accumulation of the vehicle, sulfobutyl ether beta-cyclodextrin sodium (SBECD).[2,17] Peritoneal dialysis or hemodialysis does not remove a sufficient amount of voriconazole to warrant dose adjustment.[2,17,18]
Maximum dosage	No specific maximum dosage has been defined. A critically ill 3-year-old with neuroblastoma has received 5 mg/kg q 12 hr increased q 2 days to 13 mg/kg q 12 hr then up to 21 mg/kg q 12 hr in conjunction with therapeutic drug monitoring.[19]
Additives	Each 200-mg vial contains 3.2 g SBECD.[2,20] (See Dosage Adjustment in Organ Dysfunction section.)
Suitable diluents	D5W, D5NS, D5½NS, D5W + 20 mEq/L potassium chloride, NS, ½NS, LR, D5LR.[2,20]
Maximum concentration	5 mg/mL.[2,20]
Preparation and delivery	Dilute reconstituted product to a final concentration of 0.5–5 mg/mL with appropriate diluent.[2,20] Do not administer through the same catheter or admix with other drugs, blood products, or PN.[2,20]
IV push	Not recommended.[2]
Intermittent infusion	Infuse over 1–2 hours at a maximum rate of 3 mg/kg/hr.[2,20]
Continuous infusion	No information available to support administration by this method.
Other routes of administration	No information available to support administration by other routes.
Comments	**Significant adverse effects:** The most commonly reported adverse effects in children are dose-dependent visual disturbances and increases in transaminases and bilirubin, and photosensitivity.[3] Therapy has been associated with prolongation of QT interval.[2] Serum electrolytes (potassium, magnesium, calcium) should be within range before starting therapy to reduce risk of arrhythmias.[2] Stevens-Johnson syndrome has been reported rarely.[2] **Drug interactions:** Voriconazole is metabolized primarily by CYP2C19 and less by CYP2C9 and CYP3A4; and is an inhibitor of CYP2C9, CYP2C19 and CYP3A4.[21] Voriconazole is associated with numerous serious drug interactions.[2] Consult appropriate resources for dosing recommendations before combining any drug with fluconazole. **Pharmacokinetic considerations:** Voriconazole metabolism may be variable among patients due to disease state, concomitant drug therapy and genetic polymorphisms.[2,3] Therapeutic drug monitoring is recommended to ensure optimal therapy, particularly in critically ill patients and patients receiving concomitant therapy that may affect voriconazole concentrations.[22,23] While efficacy has been correlated with trough concentrations greater than 2.05 mg/L, neurologic effects have been associated with trough concentrations above 5.5 mg/L; thus, it is prudent to adjust therapy to maintain a trough concentration between 2 and 5.5 mg/L.[3] Pediatric patients have required increased doses to achieve therapeutic drug concentrations.[19,24]

Zidovudine

Brand names

Retrovir (formerly called Azidothymidine, AZT)

Medication error potential

Look-alike, sound-alike drug names.

USP reports that zidovudine has been confused with lamivudine; no patient harm resulted.[1]

ISMP and USP report that Retrovir has been confused with ritonavir; patient harm resulted.[1,2] USP reports that Retrovir has been confused with acyclovir and Epivir; no patient harm resulted. USP also reports that Retrovir has been confused with Norvir and ritonavir; patient harm resulted.[1]

Contraindications and warnings

U.S. boxed warning: Zidovudine has been associated with hematologic toxicity (neutropenia and anemia) and myopathy. Nucleoside analogues have been associated with lactic acidosis and severe hepatomegaly with steatosis.[3]

Contraindications: Life-threatening allergic reactions to any components of the medication.[3]

Other warnings: Combivir and Trizivir contain zidovudine and thus should not be given concomitantly with zidovudine. Patients receiving interferon alpha with or without ribavirin concomitantly with zidovudine should be monitored closely for hepatic decompensation, neutropenia, and anemia.[3]

Infusion-related cautions

May cause pain or irritation at injection site.[3]

Dosage

HIV-infected children should receive aggressive antiretroviral therapy with at least three drugs. Refer to www.aidsinfo.nih.gov or 1–800-TRIALS-A for the most up-to-date information regarding HIV treatment protocols in children.[4,5]

Initiation of zidovudine postexposure prophylaxis therapy in the infant should begin as soon as possible after delivery and preferably within 6–12 hours. Therapy initiating after 48 hours is not likely to be effective.[6]

For conversion from IV to oral dosing, the oral dose is one-third greater than the IV dose.[7,8] According to the manufacturer, in *adults* the IV dosage regimen equivalent to 100 mg q 4 hr PO is approximately 1 mg/kg q 4 hr IV.[3]

Antiretroviral therapy[4–14]

Premature neonates[4]

<30 weeks gestational age (WGA): 1.5 mg/kg IV q 12 hr, then 1.5 mg/kg IV q 8 hr at 4 weeks of age.

≥30 WGA: 1.5 mg/kg IV q 12 hr, then 1.5 mg/kg IV q 8 hr at 2 weeks of age.

Term neonates and infants <6 weeks of age[4]**:** 1.5 mg/kg IV q 6 hr.

Continuous infusion of 0.5–1.4 mg/kg/hr (360–1000 mg/m^2/day) has been beneficial in children as young as 6 months with symptomatic HIV infection, especially those with encephalopathy.[11,13,14]

Prevention of perinatal transmission[4,6]**:** Maternal zidovudine 100 mg five times a day beginning at 14–34 WGA and continued through pregnancy. During labor, 2 mg/kg zidovudine IV over 1 hour followed by continuous infusion of 1 mg/kg/hr until delivery. Begin treatment in newborn as soon as possible after delivery (see recommended doses above), preferably within 6–12 hours, and continue for the first 6 weeks of life. Continuation of therapy determined by virologic test results.

Zidovudine

Dosage adjustment in organ dysfunction	Adjust dosage in patients with severe renal dysfunction.[3,5,15] If CrCl is <10 mL/min, give 50% of a normal dose.[15] May also be necessary to adjust dose or interrupt therapy in patients with significant anemia and/or neutropenia.[3,7,10,11,14] Insufficient data suggest a reduction in dose may be needed in patients with liver disease; these patients should be monitored for hematologic toxicity.[3]
Maximum dosage	640 mg/m^2/day for intermittent infusion.[7,12] 1.8 mg/kg/hr (1300 mg/m^2/day) for continuous infusion.[13,14]
Additives	None.[3]
Suitable diluents	D5W.[3,16]
Maximum concentration	4 mg/mL.[3,16]
Preparation and delivery	**Stability:** Once diluted, the solution is stable for 24 hours at room temperature and 48 hours if refrigerated at 2°C to 8°C. Because it contains no preservatives, the manufacturer suggests administering the solution within 8 hours if stored at room temperature or within 24 hours if refrigerated at 2°C to 8°C as an additional precaution.[3]
IV push	Not recommended.[3,16]
Intermittent infusion	≤4 mg/mL in D5W infused over 60 minutes.[3,16] May infuse over 30 minutes in neonates.[3,4]
Continuous infusion	Although concentration and solution type were not specified, has been given by this method.[11,13,14,16]
Other routes of administration	IM administration not recommended by manufacturer. No information available to support administration by other methods.[3,16]
Comments	**Significant adverse effects:** Anemia necessitating treatment with partial volume exchange transfusion was reported in a 36-WGA infant born via emergent c-section (secondary to decreased fetal movement) to an HIV-positive woman receiving zidovudine, lamivudine, and nevirapine who developed macrocytic anemia at 29 WGA (treated with packed RBC transfusion).[17] Severe lactic acidosis has been reported in a neonate receiving zidovudine; symptoms resolved following zidovudine discontinuation.[18] **Drug interactions:** Because zidovudine is associated with numerous drug interactions,[3] consult appropriate resources for dosing recommendations before combining any drug with zidovudine.

Zoledronic Acid

Brand names	Zometa, Reclast
Medication error potential	Look-alike, sound-alike drug names. USP reports potential for confusion between Zometa and Zofran and Zoladex.[1]
Contraindications and warnings	**Contraindications:** Previous hypersensitivity to zoledronic acid; uncorrected hypocalcemia.[2,3]
Infusion-related cautions	None noted.
Dosage	**Bone disease:** 0.0125–0.05 mg/kg over 30 minutes.[4–7] Depending on the dose, the infusion may be repeated in 6 weeks or 3 months. The incidence of hypocalcemia is decreased with the lower dose.[4] **Osteogenesis imperfecta:** 0.05 mg/kg q 6 mo was used in 17 children treated for 1–3.2 years.[8] **Osteopenia:** 0.066 mg/kg (max 4 mg) in 7 children with Crohn disease demonstrated increased lumbar spine bone mineral density z-score at 6 and 12 months.[9] There are no reports of zoledronic acid use to treat hypercalcemia in children.
Dosage adjustment in organ dysfunction	Do not use in patients with CrCl $<$35 mL/min.[2,3]
Maximum dosage	4[2] or 5[3] mg.
Additives	None.
Suitable diluents	D5W, NS.[2,3]
Maximum concentration	0.04 mg/mL.[2] 0.05 mg/mL (ready-to-infuse solution).[2]
Preparation and delivery	**Compatibility:** Incompatible with calcium containing fluids (including LR) and other parenteral drugs.[2]
IV push	Not indicated.
Intermittent infusion	Over $\geq$15 minutes.[2,3]
Continuous infusion	Not indicated.
Other routes of administration	Not indicated.

Comments

Monitoring: SCr should be measured before each infusion.[2]

Patients should be appropriately hydrated before infusion.

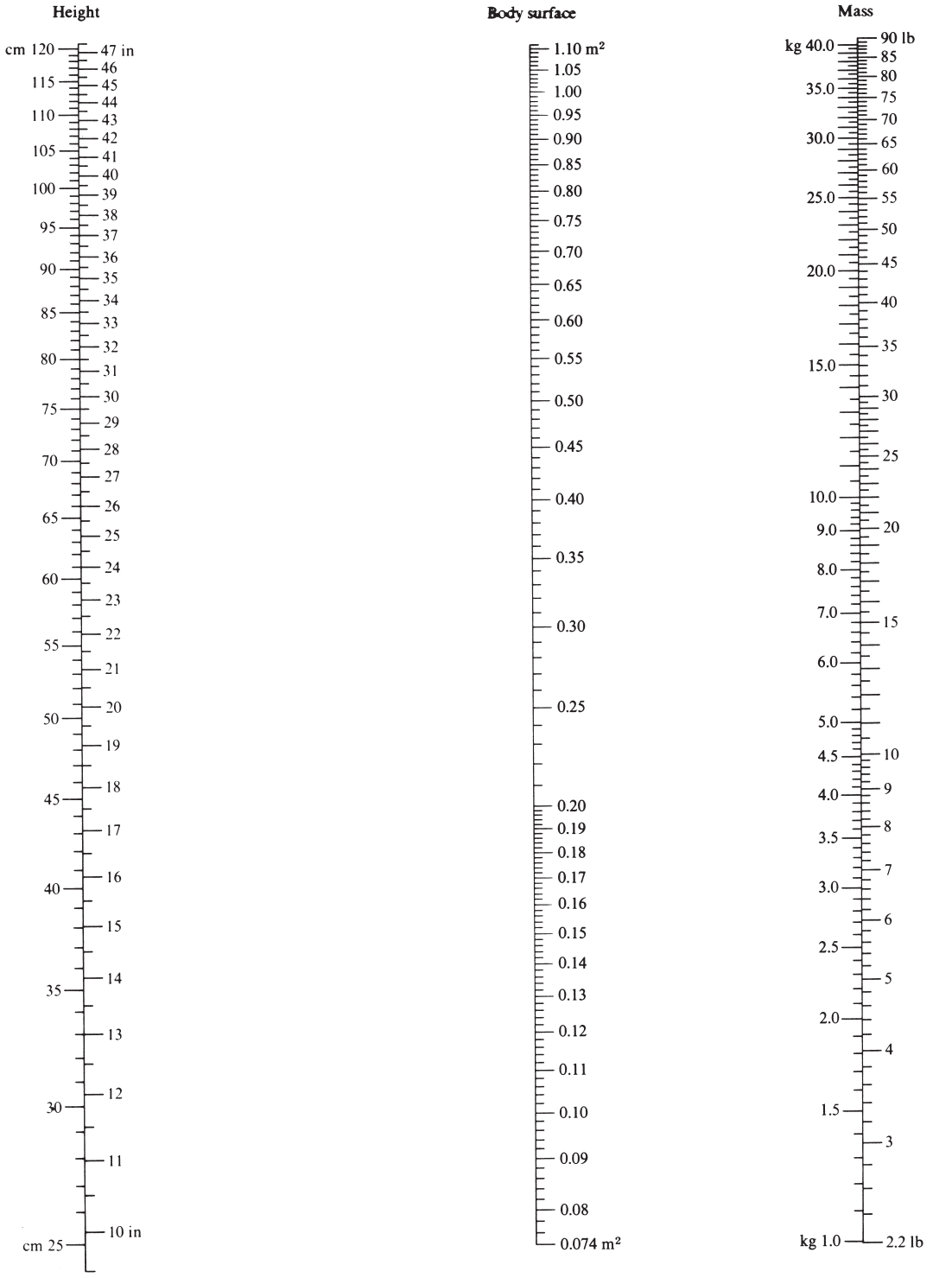
Adverse effects: A transient, low-grade fever, arthralgia, hypocalcemia, and headache within 3 days of infusion are common. The frequency of this reaction decreases with subsequent infusions.[2,3] Bone pain has also been reported frequently.[4,6] Acetaminophen administered after infusion may decrease the incidence of acute infusion-related reactions.

Osteonecrosis of the jaw has been reported in *adult* cancer patients on chemotherapy who also receive zoledronic acid. It is recommended that while on zoledronic acid invasive dental procedures should be avoided.[3] A report in children receiving pamidronate or zoledronic acid found no evidence of jaw osteonecrosis in 22 patients who underwent 38 dental procedures.[7]

Drug interactions: Aminoglycoside and loop diuretics may increase the risk for hypocalcemia.[2,3] Use nephrotoxic drugs with caution.[2,3]

Appendix A

Nomogram for Determining Body Surface Area of Children from Height and Mass



From the formula of DuBois and DuBois, *Arch. intern. Med.*, **17**, 863 (1916): $S = M^{0.425} \times H^{0.725} \times 71.84$, or $\log S = \log M \times 0.425 + \log H \times 0.725 + 1.8564$ (S: body surface in cm², M: mass in kg, H: height in cm).

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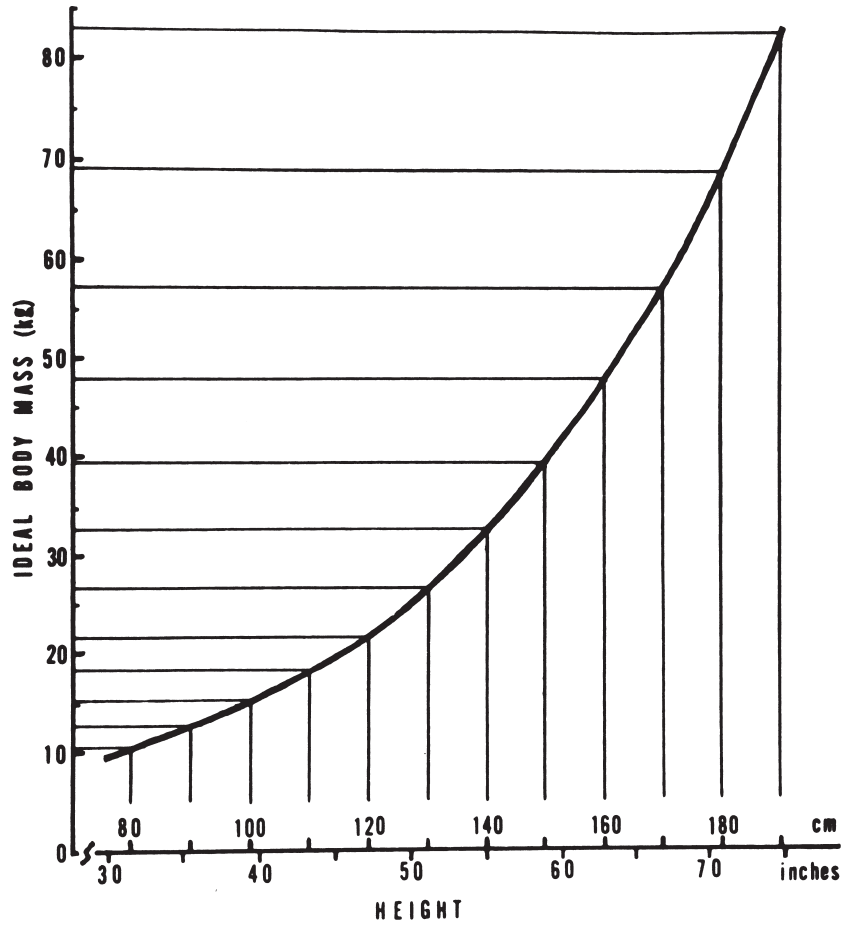
Appendix B

Nomogram for Estimating Ideal Body Mass in Children



$$\text{IBM (kg)} = 2.396\, e^{0.01863(\text{height in cm})}$$

Source: Reproduced with permission from Traub SL, Kichen L. Estimating ideal body mass in children. *Am J Hosp Pharm*. 1983;40: 107-110.

Appendix C

Additives and Antibiotic Considerations

Additives

Benzyl alcohol: Benzyl alcohol in small doses as a preservative in drugs is considered safe in newborns.[1] However, a 3-week-old, very low birth weight (710 g) infant experienced a profound oxygen desaturation that required resuscitation after the third and fourth doses of clindamycin that was subsequently related to the benzyl alcohol preservative.[2] Administration of saline flushes containing benzyl alcohol (bacteriostatic water for injection) was associated with a fatal gasping syndrome, intraventricular hemorrhage, metabolic acidosis, and increased mortality in preterm infants.[3] This should not be used in neonates. Hypersensitivity reactions to benzyl alcohol in parenteral products have been reported in *adults*.[4,5]

Paraben: Paraben preservatives may cause hypersensitivity reactions that are more common with cutaneous exposure.[6] However, one case of pruritus and bronchospasm following infusion of hydrocortisone that contained a paraben has been reported.[7]

Propylene glycol: Propylene glycol is added to parenteral drugs as a solubilizer. Rapid infusion of medications that contain propylene glycol has resulted in respiratory depression and cardiac dysrhythmias.[8] Its half-life is three times longer in neonates than in *adults*[1] and has caused hyperosmolality[9] and refractory seizures[10] in preterm neonates receiving 3 g/day.

Sulfites: Sulfites may cause hypersensitivity reactions that are more common in *adults* with asthma. Most reactions are mild but can include anaphylactic symptoms and life-threatening or less severe asthma episodes.[1,11,12] Epinephrine may be required in severe cases, and if the sulfite-free product is not available, the sulfite-preserved epinephrine should be used.[1]

Antibiotic considerations

Type I reaction to penicillin: Certain infections (i.e., syphilis) require penicillin for cure. It is recommended that a desensitization protocol for penicillin-allergic individuals should be performed in a hospital setting. This can usually be completed in about 4 hours, at which time the first dose of penicillin can be given.[13]

Patients with a history of type I reaction to penicillin should not receive beta-lactam antibiotics. Although up to 5% to 15% of patients allergic to penicillin have been reported to crossreact to cephalosporins, the true incidence may be as low as 2%.[14]

Inactivation aminoglycoside/penicillin: The beta-lactam ring of penicillins can link with an amino sugar of the aminoglycoside and inactivate the aminoglycoside.[15,16] To avoid this potential interaction, administer penicillins 1 hour before or after an aminoglycoside, adequately flush the infusion line between each infusion, or infuse them through separate lines. In vivo inactivation that is dose dependent can also occur particularly in patients with renal failure.[15,17,18] In patients with end-stage renal failure, gentamicin half-life was decreased by 22–31 hours after carbenicillin or ticarcillin was added to the drug regimen.[19]

Aminoglycosides/neuromuscular blockade: Aminoglycosides may cause neuromuscular blockade, and this effect is pronounced in patients with renal insufficiency, neuromuscular disease, and hypocalcemia.[15,20]

The effects of nondepolarizing neuromuscular blockers may be prolonged during aminoglycoside use.[20]

Cephalosporins and bleeding: The N-methyl-thiotetrazole (NMTT) side chain may inhibit vitamin K-dependent clotting factors resulting in a prolonged PTT time.[15] The coagulopathy is more pronounced in patients with renal insufficiency.[15] The non-NMTT side chain antibiotics have also been associated with bleeding in patients with renal insufficiency.

The NMTT side chain causes a disulfiram-like reaction (e.g., flushing, sweating, headache, and tachycardia) when combined with alcohol.

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Appendix D

Y-Site Compatibility of Medications with Parenteral Nutrition

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Many pediatric conditions such as abdominal wall defects of the newborn and short bowel syndrome warrant the use of parenteral nutrition (PN). Obtaining and maintaining venous access in pediatric patients complicates the administration of this form of nutrition. Many patients require multiple treatment modalities to be administered intravenously including medications, fluids, blood products, and nutrition. Clinicians must optimize available access to ensure appropriate and timely administration of all products prior to establishing additional access. This may require simultaneous administration of medications and PN; therefore, compatibility considerations become essential. It is important to recognize that compatibility reflects only the physical interactions such as formation of a precipitate and does not necessarily address stability or pharmacologic activity of the products. Published data may report both compatibility and stability; however, most evaluate compatibility alone. Currently there are multiple resources to use when answering the question of compatibility with PN. We strove to evaluate and present the available published data as a comprehensive and practical reference. We sought out primary literature regarding Y-site compatibility of multiple drugs commonly used in pediatric patients with three different PN formulas, 3-in-1, 2-in-1, and lipids alone. When conflicting results were encountered, the clinical strength was considered. When published data were not accessible, Lawrence Trissel's *Handbook on Injectable Drugs*[1] was used. Below please find each of the classifications utilized in this reference:

C Compatibility has been demonstrated. When Y-site compatibility was not available, medications compatible in solution for 24 hours were assumed to be Y-site compatible. Medications compatible with 3-in-1 admixtures were assumed to be compatible with lipids alone.[1]

I Incompatibility has been demonstrated

— Compatibility data not available

C/I Conflicting compatibility has been demonstrated and strength of the evidence supports compatible

I/C Conflicting compatibility has been demonstrated and strength of the evidence supports incompatible

Medication	Admixture Type			Comments	References	
	2-in-1	*Lipids*	*3-in-1*		*C*	*I*
Acetazolamide	**I**	**—**	**—**	White precipitate forms immediately		2
Acyclovir	**I**	**I**	**I**	White precipitate forms immediately		2,3,4
Amikacin	**C**	**C/I**	**C/I**	Visual breaking of emulsion within 1 hr in select formulations	2,3,4,5,6,7	8
Aminophylline	**C/I**	**C**	**C**		3,4,9,10	2
Amphotericin B	**I**	**I**	**I**	Yellow precipitate formed immediately		3,4
Ampicillin sodium	**C/I**	**C**	**C**		3,4,11	2,5,7,12
Ampicillin sodium–sulbactam sodium	**C**	**C**	**C**		3,4	
Atracurium besylate	**C**	**—**	**—**		13	
Aztreonam	**C**	**C**	**C**		3,4	
Bumetanide	**C**	**C**	**C**		3,4	
Caffeine	**C**	**—**	**—**		14	
Cefazolin sodium	**C/I**	**C**	**C**	Incompatible at a dextrose concentration of 25%	3,4,5,14	3
Cefepime	**C**	**—**	**—**		15	
Cefoperazone sodium	**C**	**C**	**C**		3,4,5	
Cefotaxime sodium	**C**	**C**	**C**		2,3,4,5	
Cefotetan disodium	**C**	**C**	**C**		3,4	

Medication	Admixture Type			Comments	References	
	2-in-1	*Lipids*	*3-in-1*		*C*	*I*
Cefoxitin sodium	**C**	**C**	**C**		3,4,5,11	
Ceftazidime	**C**	**C**	**C**		2,3,4,16	
Ceftriaxone sodium	**C**	**C**	**C**		3,4,13	
Cefuroxime sodium	**C**	**C**	**C**		3,4	
Chloramphenicol sodium succinate	**C**	**C**	**—**		1,5	
Chlorpromazine HCl	**C**	**C**	**C**		3,4	
Cimetidine HCl	**C**	**C**	**C**		3,4,17	
Ciprofloxacin lactate	**I**	**C**	**C**	Amber discoloration in 1–4 hr	4	3
Cisplatin	**I**	**C**	**C**	Amber discoloration in 1–4 hr	4	3
Clindamycin phosphate	**C**	**C**	**C**		4,5,11	
Co-trimoxazole	**C**	**C**	**C**		3,4	
Cyclophosphamide	**C**	**C**	**C**		3,4	
Cyclosporine	**C/I**	**C/I**	**C/I**	For 2:1, found to be compatible with Dextrose 5%/Amino Acid 4.25%, but not compatible with Dextrose 25%/Amino Acid 3.5%	3,4,18	3,4
Dexamethasone sodium phosphate	**C**	**C**	**C**		2,3,4	
Digoxin	**C**	**C**	**C**		3,4,19	
Diphenhydramine HCl	**C**	**C**	**C**		3,4	
Dobutamine HCl	**C**	**C**	**C**		2,3,4,6	
Dopamine HCl	**C**	**C/I**	**C/I**		2,3,4,19	4
Doxycycline hyclate	**C**	**I**	**I**	Emulsion disruption occurs immediately	3,5	4
Droperidol	**C**	**I**	**I**	Emulsion disruption occurs in 1–4 hr	3	4
Enalaprilat	**C**	**C**	**C**		3,4	
Epinephrine HCl	**C**	**—**	**—**		13	
Epoetin alfa	**C**	**—**	**—**		20	
Erythromycin lactobionate	**C**	**C**	**C**		5,11,13	
Famotidine	**C**	**C**	**C**		3,4,17,21,22, 23,24,25	
Fentanyl citrate	**C**	**C**	**C**		2,3,4,26	
Fluconazole	**C**	**C**	**C**		3,4,27	
Foscarnet	**C**	**—**	**—**		28	
Furosemide	**C/I**	**C**	**C**	Small amount of precipitate formed in 4 hr in select formulations	2,4,13,19	3
Ganciclovir sodium	**I/C**	**I**	**I**	Concentrations of ≥10 mg/mL resulted in precipitation within 0–30 min	29,30	3,4,29
Gentamicin sulfate	**C**	**C**	**C**		2,3,4,5,6,7, 8,11,12,13	
Granisetron HCl	**C**	**C**	**C**		3,4	
Haloperidol lactate	**C**	**I**	**I**	Emulsion disruption occurs immediately	3,13	4
Heparin sodium	**C**	**I**	**I**	Emulsion disruption occurs immediately with heparin 100 units/mL	3,13	4

Medication	Admixture Type			Comments	References	
	2-in-1	*Lipids*	*3-in-1*		*C*	*I*
Hydrochloric acid	**C**	**—**	**—**		31	
Hydrocortisone sodium/phosphate/ succinate	**C**	**C**	**C**		3,4,13	
Ifosfamide	**C**	**C**	**C**		3,4	
Imipenem–cilastatin sodium	**C**	**C**	**C**		3,4	
Immune globulin	**—/C**	**—**	**—**	Only supportive of Gammagard 2.5%; not recommended to infuse with other drugs or solutions	32	
Indomethacin sodium trihydrate	**I**	**—**	**—**			33
Insulin, regular human	**C**	**C**	**C**		3,4,13	
Iron dextran	**C/I**	**—**	**I/C**	For 2:1, found to be compatible in solution at amino acid concentrations of 2% or greater	34,35,36	35,37
Isoproterenol HCl	**C**	**C**	**C**	For 2:1, compatible with dextrose 25%/amino acids 4.25% (electrolytes were not added)	19,38	
Kanamycin sulfate	**C**	**C**	**C**		11,12,38,39	
Lidocaine HCl	**C**	**C**	**C**	For 2:1, compatible with dextrose 25%/amino acids 4.25% (electrolytes were not added)	19,38	
Linezolid	**C**	**—**	**—**	Compatible with dextrose 20%/ amino acids 4.9%; electrolytes were not added	40	
Lorazepam	**C**	**I**	**I**	Partial emulsion disruption occurs in 1 hr	3	4
Magnesium sulfate	**C**	**C**	**C**		3,4	
Mannitol	**C**	**C**	**C**		3,4	
Meperidine HCl	**C**	**C**	**C**		3,4,41	
Meropenem	**—**	**C**	**C**		4	
Methotrexate	**I**	**C**	**C**	For 2:1, hazy precipitate formed in 0–1 hr	4	3
Methyldopate HCl	**C**	**C/I**	**C/I**	For 2:1, compatible with dextrose 25%/amino acids 4.25% (electrolytes were not added); cracked the lipid emulsion in select formulations	19,38	20
Methylprednisolone sodium succinate	**C**	**C**	**C**		3,4	
Metoclopramide HCl	**I/C**	**C**	**C**	Substantial loss of natural turbidity occurred immediately in select formulations	1,4	3
Metronidazole HCl	**C**	**C**	**C**		2,3,4,13	
Midazolam HCl	**I/C**	**I**	**I**	White precipitate forms immediately in select formulations	42	3,4,13
Milrinone lactate	**C**	**—**	**—**		43,44	
Morphine sulfate	**C**	**C/I**	**C/I**	For 3:1, morphine 1 mg/mL compatible, but 15 mg/mL was not compatible; emulsion disruption occurs immediately in select formulations	3,4,13,41	4

Medication	Admixture Type			Comments	References	
	2-in-1	*Lipids*	*3-in-1*		*C*	*I*
Nafcillin sodium	**C**	**C**	**C**		3,4,5,7	
Nitroglycerin	**C**	**C**	**C**		3,4	
Norepinephrine bitartrate	**C**	**C**	**C**		3,19	
Octreotide acetate	**C**	**C**	**C**		3,4	
Ondansetron HCl	**C**	**I**	**I**	Emulsion disruption occurs immediately	3	4
Oxacillin sodium	**C**	**C**	**C**		5,7,11	
Penicillin G potassium	**C**	**C**	**C**		2,5,7,11,13	
Penicillin G sodium	**C**	**—**	**—**		5,7	
Pentobarbital sodium	**C**	**I**	**I**	Emulsion disruption occurs immediately	3	4
Phenobarbital sodium	**C**	**I**	**I**	Emulsion disruption occurs immediately	3	4
Phenytoin sodium	**I**	**I**	**—**	Heavy white precipitate forms immediately; incompatible with dextrose		1,13
Piperacillin sodium	**C**	**C**	**C**		3,4,5,7	
Piperacillin sodium–tazobactam sodium	**C**	**C**	**C**		3,4	
Potassium chloride	**C**	**C**	**C**		3,4	
Potassium phosphate	**I**	**I**	**I**	Emulsion disruption occurs immediately; increased turbidity occurs immediately		3,4
Promethazine HCl	**C/I**	**C**	**C**	Amber discoloration in 4 hr in select formulations	3,4	3
Propofol	**C**	**—**	**—**	Propofol injection contains approximately 10 g fat/100 mL	45	
Ranitidine HCl	**C**	**C**	**C**		2,3,4,13,17	
Sargramostim	**C**	**—**	**—**		46	
Sodium bicarbonate	**I/C**	**C**	**C**	Small amount of precipitate formed in 1 hr in select formulations	3,5	3
Sodium nitroprusside	**C**	**C**	**C**		3,4	
Tacrolimus	**C**	**C**	**C**		3,4	
Ticarcillin disodium	**C**	**C**	**C**		3,4,5,7,11	
Ticarcillin disodium–clavulanate potassium	**C**	**C**	**C**		3,4,13	
Tobramycin sulfate	**C**	**C**	**C**		2,3,4,5,6,7,8,11	
Vancomycin HCl	**C**	**C**	**C**		2,3,4,5,6,13	
Vecuronium bromide	**C**	**—**	**—**		13	
Vitamin K_1–phytonadione	**C**	**C**	**—**		12,47	
Zidovudine	**C**	**C**	**C**		2,3,4	

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Source: Adapted with permission from Robinson CA, Lee JE. Y-site compatibility of medications with parenteral nutrition. *J Pediatr Pharmacol Ther.* 2007;12(1):53-59.

Appendix E

Extravasation Treatment (early treatment is recommended to minimize injury)

Medication	Cold/Warm Packs × 15–20 min Several Times a Day	Antidote	Regimen
Aminophylline Calcium salts Dextrose >10% Nafcillin Oxacillin Phenytoin Potassium salts Sodium bicarbonate (8.4%) Sodium chloride (>0.9%) Tetracycline Vancomycin	Cold	Hyaluronidase	Add 1 mL NS to the lyophylized hyaluronidase vial resulting in a 150 units/mL reconstituted solution. Infuse five separate 0.2 mL SC or intradermal injections around the edge of the affected area. The needle (25 or 27 gauge) should be changed with each injection. (Some pediatric institutions dilute further by adding 0.1 mL of the 150 units/mL reconstituted dose to 1 mL NS resulting in a 15 units/mL product.)
Dobutamine Dopamine Epinephrine Norepinephrine Vasopressin	None	Phentolamine	Add 5 mg phentolamine to 9 mL NS. Inject a small amount of the dilution around the area. (Some suggest a dilution of 1 mg/mL and infusing five separate 0.1–0.2 mL injections around the affected area. The needle should be changed with each injection.) Blanching should reverse immediately. This can be repeated if necessary.
Etoposide Vinblastine Vincristine	Warm	Hyaluronidase	Add 1 mL NS to the lyophylized hyaluronidase vial resulting in a 150 units/mL reconstituted solution. Infuse five separate 0.2 mL SC or intradermal injections around the edge of the affected area. The needle (25 or 27 gauge) should be changed with each injection. (Some pediatric institutions dilute further by adding 0.1 mL of the 150 units/mL reconstituted dose to 1 mL NS resulting in a 15 units/mL product.)
Cisplatin	Cold	Sodium thiosulfate	Use of antidote is based on infiltration size and cisplatin concentration. Infiltrates <20 mL and <0.5 mg/mL cisplatin concentration: no treatment other than cool packs. In *adults*: Infiltrates >20 mL and cisplatin concentration >0.5 mg/mL use sodium thiosulfate, add 4 mL of 10% sodium thiosulfate (1/6 molar) to 6 mL SW and inject 3–5 mL.
Dactinomycin	Cold	None	
Irinotecan Topotecan	Cold		
Cyclophosphamide	Cold	Sodium thiosulfate	Add 4 mL of 10% sodium thiosulfate (1/6 molar) to 6 mL SW and inject 3–5 mL around site.

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ChlorproMAZINE HCl

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Co-Trimoxazole (Trimethoprim–Sulfamethoxazole)

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Cytomegalovirus Immunoglobulin

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Dexmedetomidine HCl

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Etomidate

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Irinotecan HCl

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Isoproterenol HCl

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Magnesium Sulfate

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Midazolam HCl

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Milrinone Lactate

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Pegfilgrastim

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Vasopressin

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Vecuronium Bromide

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